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MEDICAL PAPERS

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REGINALD HEBER FITZ.

REGINALD HEBER FITZ, whose house officers and assistants have united to celebrate his sixty-fifth birthday, has for thirty-eight years been an active factor in the development of medicine and medical education, not only in Boston, but also in the United States. Having graduated from Harvard in 1864, Dr. Fitz started his medical studies in Cambridge under the inspiring direction of the eminent physician and anatomist, Jeffries Wyman. At the same time he attended the lectures at the Harvard Medical School. The following year he came to Boston and devoted himself to study at the Medical School until April, 1867, when he became house officer at the Boston City Hospital. Here, during the service of Dr. John G. Blake, he had an opportunity to study a severe epidemic of typhus fever. After the hospital service, a few months sufficed to give him his degree, and at the end of his four years of medical training, soon after commencement, in 1868, he sailed for Europe.

Virchow had published his "Cellular Pathology" ten years before, and during the time that had elapsed the men who were to make modern medicine had developed under the inspiration of this truly epoch-making man and were in a position to give their best teaching. In Vienna under

Oppolzer and Skoda, in Berlin under Virchow, in Paris under Cornil and in London under Murchison, Dr. Fitz studied and worked. Before his return to Boston in 1870, he published a paper in Virchow's *Archives* on "Bronchiectasis."

Coming back to Boston from his period of close application in the European laboratories, his ability and attainments were at once recognized, especially by the older and powerful group of men at the Massachusetts General Hospital and the Harvard Medical School, so that in 1871 he was made Microscopist to the former and at the latter Instructor in Pathological Anatomy. His methodical German methods at autopsies were a revelation to the house officers of that day, and he early demonstrated his skill as a microscopist by making, in a tumor of doubtful origin, a correct diagnosis of syphilis, to the discomfiture of his competitors in microscopic work.

Two years later, in 1873, he entered the faculty of the Harvard Medical School as Assistant Professor of Pathology, so that for thirty-five years he has had to do constructively with medical education.

Dr. Fitz's return to Boston, it will be remembered, was coincident with Charles W. Eliot's advent to the presidency of Harvard College. President Eliot had immediately joined the radicals of the medical faculty, and aided them in putting through the changes which did away with the old lecture system and established the first graded course of medical instruction in the coun-

try. Although Dr. Fitz took no part in bringing about this change in the course of study, nevertheless as secretary of the faculty from 1874 to 1883 he did much towards setting forth the advantages of the graded continuous course of study, so that one by one the other schools of the country fell into line. He early became a member of the committee of the faculty on the course of study. and for many years has acted as chairman of this committee. In this position he has exerted an influence on medical education by many carefully considered reports which he has presented to the faculty.

As we have seen, Dr. Fitz early took rank as a pathologist, but at the same time he held the position as physician at the Boston Dispensary from 1871 to 1882, and he has, throughout his career, looked upon pathology and allied medical sciences as the handmaidens of clinical medicine rather than goddesses to be pursued for their own charms.

Dr. Fitz was appointed Professor of Pathological Anatomy in 1878, the title being changed to Shattuck Professor of Pathological Anatomy the following year. His lectures were descriptions of the changes found in regions and organs rather than of the processes bringing about the changes. The causal factors in disease were but dimly understood until the later days of his professorship, but his clear-cut, concise description of pathological changes will ever remain with his pupils.

In 1886 he presented, at the meeting of the Association of American Physicians, his most celebrated contribution to medical literature, entitled, " Perforating Inflammation of the Vermiform Appendix, with Special Reference to its Early Diagnosis and Treatment."

In the following year, 1887, he was appointed one of the Visiting Physicians of the Massachusetts General Hospital, though he maintained his position of professor of pathological anatomy at the Medical School till 1892, when he became Hersey Professor of the Theory and Practice of Physic. In this position he made no attempt to modify the old lecture system of this professorship beyond the establishment of his famous quiz-clinic, where the students' reasoning faculties were sharpened under the watchful eye of the professor himself. In his lectures selected groups of diseases were treated so that the student might have a comprehensive grasp of the underlying pathological conditions on which the whole group were dependent.

In 1900, urged on by the great development in the knowledge of disease processes and of laboratory methods for the recognition of morbid conditions, Dr. Fitz found it necessary to introduce into his department a body of assistants who should aid in the work. This group of men have taught in small sections, giving in the second year the most elementary instruction, which is supplemented in the third year by more advanced work. This system of teaching he expanded until now

in the fourth year there are courses in the hospital wards and laboratories where patients are under continuous observation by the students. Opportunity is also offered at the Medical School for original investigation on medical problems, making in all a very comprehensive course of study for the student in the Theory and Practice of Medicine.

In 1889 Dr. Fitz delivered, before the New York Pathological Society, his second notable contribution to medical literature, the Middleton Goldsmith Lecture on " Acute Pancreatitis."

Honors in the medical world have come to Dr. Fitz, and we find that he has had not only membership in the local medical societies, but a guiding hand as well, having served The Massachusetts Medical Society as Councilor for many years, and the Boston Society for Medical Improvement as president. In 1889 he was elected a Fellow of the American Society of Arts and Sciences; in 1892, Associate Fellow of the College of Physicians of Philadelphia; in 1893 Honorary Member of the Medical and Chirurgical Faculty of the State of Maryland; in 1900 Corresponding Member of the Schlesische Gesellschaft für Vaterländische Cultur; in 1904 Honorary Fellow of the New York Academy of Medicine; in 1907 Corresponding Member of Gesellschaft für innere Medicin und Kinderheilkunde of Vienna; in 1905 Harvard College conferred the degree of LL.D.; he was president of the Association of American Physicians in 1894, and in 1907 he was president of the

Congress of American Physicians and Surgeons, delivering an address entitled the " Borderland of Medicine and Surgery."

The work that Dr. Fitz has done during his active period of life has been largely critical and judicial, though always with a constructive tendency. He has formed his opinions for himself, and then bravely stood by them, even at times when they were in opposition to those of a majority of his friends or to the potent influence of the president of the university. His general position has been that of a conservative and critical councilor rather than a radical leader. His industrious habits of work have been individualistic on the whole. He has studied the works of others, rearranged their ideas or presented them in a new and truer light to the world but has not sought to be the leader of a group of students searching for new facts. Yet his personal industrious application to study has been a source of inspiration to those who have had the good fortune to be his students and assistants.

The freedom from the petty annoyances of teaching and hospital detail that is to come to him is to be considered an earnest of wise and thoughtful articles in the near future on some of the great problems that concern medical advancement.

A. K. STONE.

SOME BLOOD PRESSURE OBSERVATIONS IN ECLAMPSIA.

BY GEORGE S. C. BADGER, M.D., BOSTON,

Medical House Pupil, Massachusetts General Hospital, 1898; Physician to Out-Patients, Massachusetts General Hospital; Assistant in the Theory and Practice of Physic, Harvard University.

THE study of the blood pressure in pregnancy and the puerperium has assumed considerable importance since the development of accurate and simple sphygmomanometers. In uncomplicated pregnancy the blood pressure has been demonstrated to be within normal limits until the beginning of labor pains. With each pain there is a rise of pressure, the maximum being reached with the expulsion of the head. Following delivery there is a rapid decline of pressure to the normal. Any marked departure from this normal is pathological. Vogeler [1] gives, as the normal range of systolic pressure during pregnancy, 100 to 150 mm. of mercury. These figures he obtained from the weekly estimation of pressure in 50 pregnant women, 38 primiparæ and 12 multiparæ. His observations extended over many weeks preceding delivery, the patients being in an institution where they were under perfect control. Similar conclusions were reached by Lebedoff,[2] Stengel and Stanton,[3] Goldwater,[4] Cook and Briggs,[5] Vaquez,[6] and others. During labor they record a

rise of pressure with each pain, the maximum, as already stated, occurring with the expulsion of the head. This increased tension is called the tension of effort. The fall of pressure to the normal after labor is rapid and is permanent.

A rise of blood pressure above the normal during pregnancy or the puerperium is pathological and of diagnostic importance. Vogeler [1] says the most common causes of a peristent elevation are arteriosclerosis, nephritis and eclampsia. Moderate elevations, 150 to 180, are found in arteriosclerosis and nephritis. Extreme hypertension, 180 and over, is significant of eclampsia, even in the absence of albuminuria.

How early in the development of eclampsia the blood pressure rises I have been unable to determine from the literature. The cases reported have come under observation when the eclamptic condition was well established. Future observations may show that it is one of the earliest signs. Queirel and Reynaud [7] conclude that in pathological complications of pregnancy it gives precise information for prognosis and treatment. A continued high tension, unrelieved by treatment, makes the prognosis unfavorable. It is an absolute indication for delivery in eclampsia. Cook and Briggs [5] claim that a study of the blood pressure in eclampsia is a better guide to treatment than a study of the urine. Vogeler reports that in eclampsia the blood pressure is invariably high, and that this is the best prodromal symptom, whether albumin be present or not, and if the

pressure remain high, regardless of symptoms, the prognosis is bad.

After delivery in eclampsia, the blood pressure falls in cases going on to a favorable ending. The persistence of the high pressure demands active treatment and suggests an unfavorable outcome.

In post-partum eclampsia the pressure is high. Cook and Briggs [5] report a case. At the time of delivery the systolic blood pressure was 200, and a few hours later it rose to 210, when convulsions occurred. With treatment it fell to 125 slowly, then to 75, gradually rising to 95. Eclampsia evidently existed in this patient at the time of delivery but without convulsions. The diagnostic importance of continued high tension after delivery is illustrated by this case.

A most striking fall of blood pressure occurs in some cases of eclampsia very soon after delivery, without hemorrhage or shock to account for it. In the case just quoted the tension in the artery fell in a few hours from 210 to 75. Other similar drops in the pressure are reported. Thus Vogeler reports two cases: a primipara, age twenty-two, after the first convulsion showed a systolic pressure of 155, rising quickly to 180, when further convulsions occurred. One hour after delivery, with chloroform anesthesia, the pressure was 80, rising in twelve hours to 150. In the second case, a primipara of thirty-six, with edema of three weeks' duration, nausea and vomiting, blindness and albuminuria, a blood pressure was recorded of 200. Three hours after delivery it

was 125, and three hours later 95, a total fall of pressure in six hours of 105 mm. of mercury. During the next few days it rose slowly to 160, falling later to 110 just before death. These excessive falls of blood pressure are not the usual occurrence. The fall after delivery is rapid, but moderate in favorable cases. Thus Queirel and Reynaud [7] report a pressure of 230, rising to 240 at the time of delivery. Nine hours later it was 180, and in the following days gradually returned to normal.

The observations of the systolic blood pressure in eclampsia which I wish to record were made with a Janeway sphygmomanometer, with a twelve-centimeter armpiece. The eclamptic condition was well established in both patients when they came under observation. Each patient was studied a few days before delivery, and the effects of treatment other than delivery watched. The usual treatment for eclampsia was given. A strictly milk diet, free cartharsis, hot air baths with free sweating, produced but little effect on the blood pressure. In one instance before a hot-air bath the pressure was 222, and directly after the bath, during which there was free sweating, it was 218. Tension-lowering drugs, tincture of aconite and nitroglycerin in large and frequently repeated doses, produced almost no impression. Following delivery in both cases there was a fall in the pressure to normal, in one case a rather rapid fall, in the other a very gradual one.

CASE II. (Chart II.) IVpara, thirty-one years. Five and a half months pregnant.

Family history unimportant.

Measles as a child, otherwise always well.

One child living, four years old. Two miscarriages at seven months, cause unknown. There was nothing in the history to suggest kidney trouble, no headaches, unusual nausea or vomiting, edema, or eye symptoms. Until the present illness began was never up at night to micturate.

Entered St. Elizabeth Hospital Nov. 8, 1907. Five days before complained of pain between shoulders. The next day was in bed because of great weakness. The urine at this time was noticed to be scanty. There was severe headache and a complaint of specks before the eyes. There were no edema, no convulsions.

Physical examination showed nothing remarkable beyond a very high tension pulse (220), a sharply accentuated aortic second sound, and the uterus enlarged to correspond to a pregnancy of about five and one-half months. The urine was diminished in quantity, 850 ccm. in the twenty-four hours; there was a large amount of albumin and many casts, both hyaline and granular.

Under treatment the urine increased to 2,000 ccm., but the blood pressure remained high (225).

Nov. 11, three days after entrance, the eyes were examined and showed the presence of fresh retinal hemorrhages. Labor now began and she delivered herself on Nov. 12. Forty-eight hours after delivery the blood pressure had dropped from 223 to 180, and marked improvement had taken place in the patient's condition. From Nov. 18 to 23 there was a febrile condition without obvious cause, yet during this the blood pressure continued to fall. A complete recovery

was not made in this case. The lowest point reached in the blood pressure was 150 on the 23d of November. At this time she was allowed to sit up in bed and gradually to get up and about. Coincident with this the blood pressure rose again to 170 and remained about that point up to the time of discharge from the hospital. The urine was never free from albumin, the eyesight remained considerably blurred.

Three months later she reported at my office, feeling fairly well. Vision had improved somewhat, but was not yet good. She tired easily, was up two and three times at night to micturate. The urine was pale, of 1,012 specific gravity, and contained a good trace of albumin. The blood pressure was 175. The heart was very slightly hypertrophied, the aortic second was sharply accentuated and ringing.

CONCLUSIONS.

1. The blood pressure in eclampsia is high, and of diagnostic and prognostic importance.

2. In spite of improvement in subjective symptoms and increase in the quantity of urine, the blood pressure may remain high.

3. In which case the prognosis is grave, and labor ought to be induced.

4. The continuance of high blood pressure during the puerperium warrants a grave prognosis as to complete recovery.

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TWO CASES OF ATYPICAL LEUKEMIA.

BY WILLISTON W. BARKER, M.D.,
Medical House Pupil, Massachusetts General Hospital, 1908.

I. ACUTE fatal anemia with terminal blood-picture of lymphatic leukemia.

C. C., female, twenty-five, married, Italian, housewife, entered the Massachusetts General Hospital on the service of Dr. E. G. Cutler, June 1, 1907. Family history and previous history negative. Habits and hygiene good. Eight weeks before entrance she began to have pain in back, legs, shoulders and head, not involving joints, at times requiring morphia for its relief. Two weeks before entrance she began to be pale and yellowish, weak, and short of breath on exertion. For ten days she had been in bed; had lost from 15 to 20 lb. in weight. She had several times seen small red and black spots appear suddenly on neck and arms, later disappearing. One week before entrance her throat began to be sore.

Physical examination showed that she was well developed and nourished, but her skin and mucous membranes were pale. Pupils were equal, reacted normally. Left tonsil was reddened, swollen and covered with whitish exudate. Heart's apex impulse in fifth space, four inches to left of mid-sternal line; left border of dullness corresponded; no enlargement to right. Sounds of good quality; no murmur heard. Pulse of rather low tension. Lungs normal. Abdomen normal. Liver and spleen easily felt; liver dullness from sixth rib to costal margin. Slight edema of ankles

present. No glandular enlargement. Urine high-colored, acid, 1,017–1,024, without albumin, sugar or bile. Urea, 2.99–2.02%. Sediment showed only squamous epithelial cells. Stool gave negative reaction for blood by guaiac test; no ova or parasites found. Temperature ranged from 99° to 97.4° F.; pulse from 88 to 110; respiration from 18 to 26. Cultures from the throat were free from diphtheria bacilli, and the exudate disappeared a few days after entrance.

Patient felt very much better after coming to the hospital and was discharged at her own request, June 14, " much relieved," but without any notable change in physical signs.

She re-entered the ward on the service of Dr. H. F. Vickery, July 11, 1907, with a story of progressive weakness ever since discharge. She complained bitterly of pain in the long bones. She had had a normal menstrual flow two weeks after leaving the hospital.

The following changes were observed in physical signs. The skin had become lemon yellow and the mucous membranes exceedingly pale. There were small ecchymoses on neck, front of chest, right shoulder and abdomen. Heart's apex impulse in fifth space five inches to left of mid-sternal line; loud systolic murmur heard all over precordia; pulmonic second sound markedly accentuated. Liver edge questionably felt. Spleen felt two inches below costal margin, hard and tender. Motions of spine limited, apparently by pain and spasm. Moderate tenderness over long bones. Urine pale, acid, 1,010, with a very slight trace of albumin, without albumose, sugar or bile. Urea 1.39%. Sediment showed an occasional red or white blood corpuscle; no casts seen. Stools bloody, with masses of clay-colored feces. Guaiac test for blood strongly positive. Microscopic examination showed fat and

fatty acid crystals, red and white blood corpuscles. Temperature fell gradually from 103.4° at entrance to 98.4°; pulse ranged from 110 to 140; respiration from 30 to 50. For blood examinations see table.

Patient vomited frequently and her bowels moved from one to four times daily; vomitus once was bloody. She failed steadily and died July 14 after two hours of wild delirium. Autopsy not obtained.

Five examinations of the blood were made; the last one, dated July 14, was completed about half an hour before death. The percentages given in this examination are based upon a differential count of 1,000 white cells, the others upon differentials of 200. The large lymphocytes were mostly of medium size; they were several times observed to be phagocytic for erythrocytes. (See Table of Blood Counts.)

The absence of an autopsy makes the case incomplete and renders any absolute diagnosis impossible, but such evidence as is at hand makes the diagnosis of acute lymphatic leukemia most probable. The striking features are: (1) The acute course, under four months; (2) the extreme and progressive anemia; (3) the overwhelming increase, both relative and absolute, in the number of large lymphocytes; (4) the practical absence of platelets in the later examinations; (5) the absence of glandular enlargement. Several similar cases of acute anemia with terminal lymphemia have been reported (Litten, Luce, Körmöczi and others); in some of them the marrow has been examined and has shown lymphoid instead of erythroblastic " hyperplasia " or " degeneration." A case of myelocytic leukemia was

Table of Blood Counts.

	Hb. Per cent.	Erythrocytes.	Leucocytes.	Per cent in count of 200.					Seen in Count		Platelets.	Stippling.	Polychromatophilia.	Poikilocytosis.	Macrocytosis.	Microcytosis.
				Poly. Neut.	Lymph. Large. Small.	Poly. Eos.	Mast cells.	Myelocytes.	Blasts Nor.	Blasts Meg.						
June 1.....	55	2,136,000	3,300	53	45	0	1	1	7	1	diminished	slight	moderate	moderate	little	much
„ 10....	55	2,044,000	4,400	52	48	0	0	0	1	5	rare	none	marked	„	„	„
„ 14....	45	2,580,000	6,000	37.5	59.5	1	0	2	2	2	very rare	slight	„	„	„	„
July 12	15	1,072,000	14,700	6.5	92.5	1	0	+	6	2	very rare	marked	„	„	„	„
„ 14	15	816,000	91,500	6.1	92.9 / 84 / 8.9	0.1	0	0.9	6	9	* „	„	„	„	„	„

*In count of 1000 whites.

reported in 1907 by Hunter in which the blood picture changed in three weeks from pernicious anemia to leukemia, the leucocyte count having risen in that time from 6,000 to 290,000. In 1907, also, a case was reported by Sluka which presented in life the blood of pernicious anemia but showed at autopsy the bone-marrow of large cell lymphatic leukemia. It has been suggested by Dr. J. H. Wright that in the case here reported the disease was wholly a hyperplasia of large lymphocytes or pre-lymphocytic cells in the marrow, manifesting itself at first only by a reduction in the number of circulating erythrocytes and platelets and the attendant clinical symptoms and signs of anemia, but revealing its existence just before death through the escape or discharge into the blood-stream of some of the essential factors, the lymphocytes. Without microscopic examination of the marrow such a theory " is very largely conjecture." As for the absence of glandular enlargement, so many cases of lymphatic leukemia without glandular enlargement have recently been reported that this case is in very slight degree noteworthy in that respect.

The classification and nomenclature of the so-called primary blood diseases is the subject of lively discussion. It is not yet determined whether there is a disease " leukanemia " with the red cells of pernicious anemia and the white cells of leukemia, or whether fatal anemia with very late lymphemia or entirely without lymphemia but with lymphoid bone marrow shall be called

" pseudo-leukemia." In view of the established usage of the latter term in respect to Hodgkin's disease it seems more reasonable to us to call it " aleukemic leukemia." For further discussion of this subject reference may be made to the writings of Pappenheim, H. Hirschfeld, and others published especially in *Folia Hæmatologica.*

II. Acute fatal anemia with hematoma of knee, extreme terminal leucocytosis and hyperplasia of megakaryocytes.

F. M., male, eighteen, single, American, chair-maker, entered the Massachusetts General Hospital on the service of Dr. C. A. Porter July 18, 1907. Family history and previous history negative. Five months previous to entrance he noticed a hard tender swelling just above right knee, extending slowly until it involved the whole knee and thigh; not very painful until four weeks before entrance, when it became exceedingly painful and tender. He gave up work at once and went to bed on account of the pain; since then his appetite had failed, he had grown pale and he had lost much weight and strength.

Physical examination showed that he was frail, emaciated, and very pale. Reflexes normal. Tongue clean. Throat and lungs normal. Heart enlarged slightly to right, not to left. Systolic murmur heard at apex, not transmitted. Pulmonic second sound accentuated. Abdomen normal except for edema and ecchymoses in right flank. Liver and spleen not felt. No glandular enlargement found. Right thigh and knee swollen, hot and tender, but not red. Fluid present in and about joint. Pale yellow ecchymoses in skin over thigh. No edema nor purpura except as above noted. Urine normal in color, acid, 1,023,

without albumin or sugar. White count 55,000. Temperature 101.8°, pulse 112, respiration 24.

The patient was admitted from the accident room to the ward with a probable septic knee. On the following day the knee-joint was aspirated by Dr. Jones, who withdrew ℥viii of dark, bloody fluid. Stained smears showed red blood cells, polynuclear leucocytes and fibrin; no micro-organisms. The thigh was then opened above the knee and several ounces of similar fluid were obtained from a cavity extending down to bare bone. The bony surface showed no evidence of sepsis or neoplasm. Cultures from both specimens of fluid remained sterile after seventy-two hours of incubation.

The patient failed gradually after operation, vomiting frequently and oozing serum into the dressing. His temperature varied from 98.4° to 102.6° F., his pulse from 112 to 138, and his respiration from 22 to 31. He was seen in consultation July 22 by Dr. J. J. Minot and July 24 by Dr. H. F. Vickery, who concurred in the diagnosis of acute primary anemia. He died quietly July 25. No autopsy was obtained, but Dr. Oscar Richardson was permitted to remove sufficient bone marrow from the exposed end of the femur to make smears; it was unfortunately too soft to be removed through the wound in condition to be hardened and sectioned. The following examinations were made of the blood:

July 19. Hb. 55%. Whites 63,800. Polynuclear neutrophiles 91%, large lymphocytes 8%, small lymphocytes 1%, in a count of 100 white cells. The red cells showed some variation in size and shape, with marked polychromatophilia and stippling, and one megaloblast and one normoblast were seen while counting.

July 20. Whites 106,000.

July 22. Whites 78,400. Reds 1,520,000.

July 24. Hb. 15%. Reds 1,080,000. Whites 222,000. Polynuclear neutrophiles 91.46%, large lymphocytes 3.07%, small lymphocytes 2.78%, polynuclear eosinophiles 0.29%, neutrophile myelocytes 2.4%, mast cells absent, in a count of 1,000 white cells. Platelets 1,188,000. The red cells showed considerable variation in size and shape, with a tendency to microcytosis; stippling and polychromatophilia were marked. Seventy-nine megaloblasts and 74 normoblasts were seen in the count of 1,000 whites, or about 34,000 per cubic millimeter. Many of them showed mitotic figures. Some idea of their frequency may be obtained from the fact that as many as eleven were seen in one field of a thin smear with oil-immersion objective and high-power eyepiece.

The bone marrow was soft, semi-fluid, the color of raspberry jelly. The smears showed an apparently normal number of erythroblasts and myelocytes, mostly of small size, and very few polynuclear neutrophiles. The giant cells, on the contrary, were markedly and strikingly more numerous than in smears of normal bone marrow; they also were of small average size. It is interesting to note relation between the number of giant-cells in the marrow and the number of platelets in the blood. According to the conclusions of Wright, the blood platelets are detached fragments of the cytoplasm of megakaryocytes (giant cells of bone marrow). If the imperfect examination of bone marrow in smears is a fair index of the general condition of the marrow, the co-existence of increased platelets in the blood and giant cells in the marrow is in harmony with the conclusions of Wright.

No case exactly similar to this has been found in the accessible literature. Large hematomata requiring operation are not very rare in severe anemias and leukemias. Milward reports a case in which there were swellings about the knees supposed to be scorbutic; the case afterward proved to be lymphatic leukemia. Barié and Salmon also report a case of enormous hematoma of the shoulder in a case of acute leukemia. The case reported here was at first supposed to be sepsis; this was disproved by microscopic examination of and by cultures from the fluid removed from the swelling; it was then considered to be perhaps a tumor of bone which had undergone degeneration, but neither the appearance of the bone in the neighborhood nor the microscopic examination of the marrow supports this theory. In the absence of a complete autopsy we are again reduced to conjecture, but the cellular elements of the marrow, taken with the blood picture, point to the marrow as the most probable primary seat of disease.

It has been suggested that there was a general hyperplasia of the bone-marrow cells, and that the terminal drain, perhaps of the operation and subsequent oozing, drew out the erythroblasts, platelets and polynuclears into the blood-stream but left the giant cells *in situ* because of some mechanical obstruction. It is undoubtedly true that rapid changes took place in the blood just before death and that a very great increase occurred in the number of circulating polynuclears

and erythroblasts, but there is no evidence in the smears of marrow of increased formation of those cells, while there is to be seen a great excess of giant cells. In fact, the giant cells may be considered to have interfered with erythrocyte and perhaps with polynuclear leucocyte generation in some such way as the lymphocytes do in acute lymphatic leukemia. In other words, this case may be considered to be a "leukemia" of the megakaryocytes. It is to be said, however, that this is only one way of explaining a somewhat obscure and, in the absence of autopsy, an incomplete clinical and histological picture. Just where the case is to be placed in any system of classifying diseases of the bone marrow is a matter for discussion. If the term "aleukemic leukemia" is admissible, if "leukemia" is taken to mean merely a primary hyperplasia of one or more of the cellular elements of marrow without regard to leucocythemia, why is not "pernicious anemia" a "leukemia"? "That way madness lies." It is likely that in future a system of nomenclature to include all the myelogenous diseases may be adopted, with divisions allotted to erythroblastic, leucoblastic and platelet-forming cells.

In conclusion the writer wishes to acknowledge his indebtedness to Drs. Cutler, Vickery, Porter and Jones for permission to report the cases, and to Dr. J. H. Wright for kindly and enlightening aid in their study.

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ON THE TOXIN OF ECLAMPSIA.

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I. EARLIER RESEARCHES ON ECLAMPSIA.

PUERPERAL eclampsia has been for many years the subject of careful clinical and pathological study. The literature on eclampsia is very extensive and goes back to the early forties. But in spite of this fact very little real progress has been made in determining the cause of the disease. It is to-day considered a decided pathological entity associated with lesions so characteristic that after death, at least, there can be no doubt about the diagnosis. As to the diagnosis during life, it is a very different matter; personally I have no doubt that many cases of uremia and epilepsy are diagnosticated as eclampsia, and when the patients recover there is no means of knowing that the diagnosis was not correct.

Based on the presence of albumin in the urine, the theory of Frerichs, who pronounced eclampsia a condition secondary to uremia, was for many years the accepted teaching. Frerichs attributed the symptoms to a poisoning of the blood through the retention of urea and the conversion of the latter into ammonium carbonate. We know to-day, however, that cases of eclampsia without

albuminuria or signs of kidney disease occur not infrequently. Rosenstein attributed the convulsions to anemia of the brain; others (Cohnheim, Spiegelberg, Schroeder) sought the cause of eclampsia in a spasm of the arteries in the kidneys and brain, produced reflexly by the pregnant uterus. Halbertsma assumed that the convulsions were due to disease of the kidneys secondary to pressure upon the ureters. But many cases of eclampsia have come to notice where each and all of these conditions were absent.

Ludwig and Savor revived a modification of Frerichs' original uremia theory by their assumption that eclampsia was an auto-intoxication due to the retention of poisonous products of metabolism which the kidneys were functionally unable to eliminate from the system. These authors chose carbamic acid and ammonium carbamate as the materia peccans in place of the ammonium carbonate of Frerichs. Vollhard succeeded in completely disproving this theory. Numerous theories, some of which have sought to account for eclampsia as due to anomalies of structure and function of the blood vessels and nerve centers (von Herff, Kundrat, etc.), and others which sought the cause in a bacterial invasion or bacteriotoxic poisoning of the system (Albert, H. Mueller, Levinowitch, Stroganoff) have shared the fate of the earlier theories.

Of course, physico-chemical methods of investigation have also had their day. The freezing point of the blood and urine of normal and

eclamptic pregnancies was studied by many authors (Koranyi, Kroenig, Fueth, Szili, Dienst, J. Veit, Schroeder, Caspar and Richter). They found that in three fourths of all cases of pregnancy the urine shows an insufficient molecular concentration and consequent insufficient diuresis, which reaches its lowest level at childbirth. Immediately after childbirth the molecular concentration of the urine begins to rise rapidly. The molecular concentration of eclamptic urines was found by most authors to be practically that found in normal cases; Schroeder alone found values in eclampsia which are far below those given as the lowest for the molecular concentration of the urine in normal pregnancies. It is a remarkable fact that with such decidedly insufficient diuresis the urine may be absolutely free from albumin.

Investigations on the toxicity of the blood and urine by the so-called Bouchard method have not yielded results of any value. In fact, Schuhmacher found that the urine of non-pregnant women was equally as toxic as that of normal pregnancy or eclampsia. This he found also to be true of the blood sera of normal and eclamptic women when they were injected intravenously into rabbits.

The bio-chemical method of investigation was used in cases of eclampsia by Halban and Langsteiner. Applying the methods of Ehrlich and his pupils they studied the action of parental and fetal blood on normal human blood, on the blood of rabbits and on bacteria (hemolysis, agglutina-

tion, bactericidal action), as also the influence of the two kinds of blood on fermentative (trypsin) and toxic processes (agglutination with abrin and ricin). Finally they attempted to determine the quantity of agglutinable and precipitable substances in the parental and fetal blood. As a result of their work Halban and Langsteiner, as also Veit, found slight but distinct bio-chemical differences between the mother's blood and that of the fetus; and Halban was able to show that a reciprocal agglutination and even hemolysis is possible between parental and fetal blood.

The careful studies of Stumpf and Winkel, and after them of Jürgens, Schmorl and Lubarsch, have thrown much light on the nature of the eclamptic lesions. Stumpf and Winkel were the first to call attention to the fact that the fetus usually shows kidney and liver lesions similar to those of the mother. Schmorl discovered the fact that eclamptic blood contained from five to eight times as much fibrin as the blood of normal pregnancy. He also laid great stress on the peculiar nature of the liver lesions as well as on the almost universal thrombosis present in cases of death from eclampsia. To quote from Williams: "In eclampsia, as was first pointed out by Jürgens, Schmorl and others, the lesions consist in hemorrhagic necroses occurring in the portal spaces, dependent upon thrombotic processes in the smaller portal branches. At first they are sharply limited to the portal spaces, but as they enlarge, they invade the lobules

from the periphery toward the center; and are so characteristic that their mere presence justifies the diagnosis of eclampsia without any clinical history of the case."

J. H. Wright does not agree with Schmorl in attributing the focal liver necroses to thromboses. While he concedes the fact that the necrosis seems to proceed from the periphery of the lobule toward the center, he maintains that the lesions are not necessarily associated with thrombosis. To Wright the most striking feature of the eclamptic liver section is to be found in the character of the necrosis, which is always associated with the formation in large quantity of a peculiar reticulated fibrinoid substance. This substance, according to Wright, is never seen in such remarkable distribution and quantity in any other pathological condition of the liver.

The occurrence of an abnormally large quantity of fibrin in the eclamptic blood has led Dienst to base a method of diagnosticating eclampsia on the determination of fibrin in the blood of pregnant women. If the fibrin test is positive Dienst immediately begins a treatment for eclampsia which consists in the introduction of the largest possible quantities of alkaline solutions into the system, together with hot-air baths, catharsis, etc. He claims in this manner to be able to prevent in practically every case the occurrence of convulsions and coma.

Schroeder, who has made a special study of the blood pressure in cases of eclampsia, comes to the

conclusion that in many cases of this disease the blood pressure is practically normal and that on this account the determination of the blood pressure is of no value as a means of diagnosis.

Weichardt, a pupil of Schmorl, and Pilz have recently obtained most interesting results. They argued that since both the mother's tissues and those of the fetus showed the lesions of eclampsia, the toxic element was probably produced in and disseminated from the placenta. In order to eliminate from the placental tissues any antitoxin which the blood might contain, they removed the blood as completely as possible from the fresh placenta (perfusion with physiological salt solution at body temperature through the umbilical arteries) and extracted the finely divided organ with physiological salt solution. This extract they found to contain a most powerful toxin (syncytiotoxin) which was very virulent to rabbits. One to three cubic centimeters of a total extract of 30 ccm. (obtained from 50 gm. of crushed placenta) given intravenously to rabbits, caused death to occur very rapidly due to paralysis of respiration. The heart continued in each case to beat for some time after the cessation of respiration. By injecting very small, non-lethal doses of the active extract into the mesenteric vein of rabbits, Weichardt and Pilz succeeded in producing an immunity to the poison. Their active solution was, however, very thermolabile, since heating it at 60° on the water-bath for a short time was sufficient to render it ab-

solutely innocuous. It is to be noted that Weichardt and Pilz obtained their active solution from normal placentas.

I began my work on eclampsia in 1896, when I was assistant in pharmacology at the University of Strassburg. In attempting a solution of the problem I approached the subject from the point of view of the pharmacologist, that is to say, my aim was to determine whether or not the blood of eclamptic women, or that of the eclamptic placenta, contained an active, non-proteid body, which might perhaps be isolated and recognized to belong to one of the established pharmacological groups of poisons, or to form a representative of a new group.

With this end in view I proceeded in a manner radically different from that of the serologists of the Ehrlich school. It was my object to obtain proteid-free solutions; this necessitated the application of heat with consequent inactivation or precipitation of serum or tissue-juice constituents like the body of Weichardt and Pilz. To test the activity of my solutions I made use of intravenous injections into rabbits. In each instance but one I have given the chief clinical data of the case from which the material was derived. It will be seen from the histories that the clinical picture of the case gives no indication of the presence or absence of the toxin in the blood and tissues.

II. PERSONAL OBSERVATIONS.

A. — My first material was obtained from the Frauenklinik in Strassburg, and consisted of 250

ccm. of blood drawn by venesection from a patient who, according to Professor Fehling, had a typical case of eclampsia.

The blood was clotted when I received it; I was, therefore, obliged, after removing the serum, to triturate the clot with a little water and pure washed sand. The finely divided clot was transferred to a filter and thoroughly extracted, first with cold, then with hot distilled water. The filtrate was united with the serum, the whole barely acidulated with acetic acid and then heated in a large evaporating dish on the water-bath for several hours. When the red color of the fluid had changed to a light straw color the finely divided coagulum was collected on a filter and thoroughly washed with hot water. The clear filtrate and wash water were united and again heated on the water-bath. After a certain degree of concentration had been reached, a second finely divided coagulum was formed; this was again removed and the same process of fractional coagulation was continued until the resulting fluid amounted to about 10 ccm. of a reddish-brown liquid which did not yield the faintest biuret reaction, and which was therefore free from proteid.

Feeling that the fluid if active at all would be only slightly so, I slowly injected nearly the entire quantity into the large vein of a rabbit's leg. As I was completing the injection the rabbit had one violent convulsion and died. Only about 1 ccm. of the solution remained; this I injected into the ear vein of another rabbit. The second animal did not seem in the least disturbed by the injection; a few moments after it he ate food in a normal manner. This was at about 3 o'clock in the afternoon; at 6 P.M. I examined the animal and found it apparently normal. The next morning I learned from the attendant that at 9 P.M. he had

found the animal dead, but still warm. The rabbit had probably died very shortly before 9 P.M., death having occurred in about six hours.

Post-mortem section of the two rabbits showed no macroscopic changes; microscopic sections of the organs were not made.

B. — On March 14, 1907, I received a placenta from the Boston Lying-in Hospital. The history of the case is as follows:

E. S., Russian Jewess, twenty-seven, Ipara. Brought to hospital in state of coma on the evening of March 13. Indefinite history of convulsions, headaches for past two to three days. Catheter specimen of urine showed slightest possible trace albumin, no sugar, no renal elements. Left hemiplegia, left pupil widely dilated. Reflexes normal, no Babinsky, no Kernig's. Temperature 101°, pulse 112.

Patient was delivered under ether with forceps at 12.55 A.M., March 14. After delivery patient continued comatose and died at 10 P.M. A post-mortem section, which was performed at the Massachusetts General Hospital by Dr. O. Richardson, showed:

Disseminated areas of hemorrhage in the brain. Thrombosis of right lateral sinus. An area of softening on the floor of the third ventricle. Acute degeneration of the kidneys. Acute degeneration of the liver with hemorrhages. Hemorrhagic edema of the lungs. The liver findings are not those typical of eclampsia. (J. H. Wright.)

The placenta was finely divided in a meat chopper and extracted with large quantities of distilled water until the strained extracts were practically colorless. The blood and the tissue extracts were united with the total wash waters, barely acidified with acetic acid and heated in a large porcelain dish on the water-bath. The

proteids were removed by fractional coagulation and the solution concentrated as described above. The final reddish-brown fluid obtained showed a faint acid reaction and possessed a peculiar, not agreeable, odor.

EXPERIMENT 1. March 16. Rabbit (2 kg.) given, 3 P.M., 4 ccm. placental fluid into vein of ear. No immediate symptoms. 5 P.M., animal refuses food, crouches in somnolent condition in a corner of the cage and does not react to stimuli. Respiration 140. Pulse too rapid to count. Temperature 105°.

March 17. 8 A.M., rabbit found dead in cage, still warm; death had therefore occurred in about eleven hours. Sections of the liver show necrotic areas with diffuse hemorrhages.

EXPERIMENT 2. March 17, rabbit (1.5 kg.) given, 5 P.M., 1.5 ccm. subcutaneously. No action.

March 18. Animal well.

March 19. Animal well. 3 ccm. solution given subcutaneously. No action.

March 20. Animal well.

EXPERIMENT 3. March 20. Guinea pig given, 5 P.M., 1 ccm. solution subcutaneously. No immediate symptoms.

March 21. Animal refuses all food; crouches in corner of cage with fur bristling.

March 22. Animal normal.

March 23. Animal normal. 2 ccm. solution subcutaneously. No action.

March 24. Animal normal.

EXPERIMENT 4. March 21. Rabbit (2 kg.) received, 11 A.M., 1.5 ccm. dilute solution intravenously; 5 P.M., animal seems affected, refuses all food and does not react to stimuli.

March 22. Animal decidedly ill, refuses all food; labored, rapid respiration.

March 23. Animal still ill, but not so prostrated as day before; 1 ccm. fluid injected into vein of ear.

March 25. Animal very ill; somnolent; hind legs appear to be somewhat paralyzed.

March 26. Animal a little brighter; makes weak effort to eat. Intravenous injection of 3 ccm. fluid.

March 27. Animal shows decided dyspnea; lies in unnatural position with outstretched hind legs.

March 29. Animal died during night.

Post-mortem sections of liver show multiple necrosis, but no typical hemorrhages.

C. — On Sept. 20, 1907, I received from the Boston Lying-in Hospital a placenta with a clinical history as follows:

L. C., Italian, eighth pregnancy. No eclamptic history with any of earlier confinements. Nine months pregnant. No symptoms until night before. No headaches, no edema or eye symptoms. 10.30 P.M., Sept. 18, epigastric pain. 5.30 P.M., Sept. 19, first convulsion followed at intervals by nine others, the last 3 of which occurred in the hospital. Convulsions called "typical eclamptic." Very little edema of legs, none of face and hands. Unconscious; respirations good, not stertorous.

Urine: bloody, albumin ¼%. Sediment: many hyaline and fine granular casts; much blood. Case delivered. Recovery.

The placenta was treated as described under *B* and a proteid-free fluid was obtained. With this the following tests were made:

EXPERIMENT 1. Sept. 22. Rabbit (1.5 kg.) receives, 11.30 A.M., 2 ccm. fluid intravenously. 2 P.M., animal appears stupid; is easily hypnotized to retain any position and is roused with difficulty only from the hypnotic sleep. Respiration rapid and labored. 5

P.M., hypnotic condition still more pronounced. Respirations labored, 184. Pulse not obtainable on account of rapidity. Temperature 104.5°.

Sept. 23. Animal found dead.

Sections of liver show necrotic areas with diffuse hemorrhages.

EXPERIMENT 2. Sept. 25. Rabbit (2 kg.) receives, 3 P.M., 1.5 ccm. concentrated solution intravenously. 3.30 P.M., animal appears normal. 4.30 P.M., animal decidedly affected; appears to fall asleep spontaneously; does not react to stimuli. Respirations very rapid. Pulse too rapid to count. Temperature 105.2°. 5.30 P.M., animal dead.

Sections of liver show considerably cloudy swelling, but no typical hemorrhages.

D. — On July 22 I received from the State Hospital at Tewksbury, a placenta with the following history:

Ipara, nineteen. For several weeks under treatment for albuminuria, which has somewhat improved. False pains July 17. July 20, 3 P.M., convulsions of five minutes' duration (number not given). 3.30 P.M., delivered under ether with forceps; no more convulsions. Urine at birth, clear, considerable in quantity, trace of albumin.

The placenta of this case was treated as described above (*B*). With the proteid-free extract experiments were made on rabbits. *The solution was found to be absolutely inactive.*

E. — On March 5, 1908, I received a placenta from the Boston Lying-in Hospital accompanied by a history as follows :

H. A. H., twenty-four, Ipara. Last menstrual period in June, 1907. March 4, 1908, patient was seized in the afternoon with vomiting and pain in the epigastrium. Patient was given castor oil with the desired result.

Pain and vomiting ceased. Early in the morning of March 5, patient was seized again with pain in epigastrium, very severe this time, and vomiting, as also blindness. She had one convulsion. She was sent to the Lying-in Hospital, and delivered at 11.30 A.M. Recovery. *The proteid-free extract obtained from this placenta was also quite inactive.*

Several other placentas which I received and which were accompanied by a clinical history strongly suggestive of eclampsia yielded an inactive extract. Extracts of numerous normal placentas were invariably found inactive.

PREPARATION OF ACTIVE BODY IN PURE STATE.

The remainder of the fluid from case C was completely precipitated with a large excess of alcohol. The doughy, white precipitate was collected on a filter and thoroughly washed with alcohol. The alcoholic filtrate (*A*) was evaporated on the water-bath with constant additions of water until all the alcohol had been removed.

EXPERIMENT 1. The residue, amounting to a few cubic centimeters, was given intravenously to a rabbit. No action.

The precipitate produced by the alcohol was dissolved in about 50 ccm. of water and treated on the water-bath until all traces of alcohol had disappeared. The solution was tested as follows:

EXPERIMENT 2. Oct. 6, 1907. Rabbit (2 kg.) receives, 4 P.M., 1.5 ccm. of a dilute solution intravenously. At first animal appears normal. 4.30 P.M., respiration labored and rapid; animal stupid and easily hypnotized in most unnatural positions. 4.45 P.M., respiration still more labored; animal very restless, keeps turning around in a circle. 4.50 P.M., animal

apparently very ill, assumes position as if about to jump, and remains in this position for hours. Respiration 104. 5.00 P.M., animal drops to sleep spontaneously, awakening just as it is about to fall over.

Oct. 7. Animal fully recovered.

Having found the solution of the alcohol precipitate to be active, I attempted to reprecipitate the active substance from solution. The solution was fractionally precipitated with alcohol, and each fraction obtained tested for pharmacological action. None of the fractions obtained showed any action. The remaining solution, to which a large excess of alcohol had now been added, showed a marked turbidity, but yielded no further precipitate, not even on several days' standing. I therefore added a large amount of ether to the solution, thereby increasing the turbidity. No precipitate was formed. The solution, well covered, was set aside. In the course of a week, beautiful, colorless needles began to form. In order to insure complete separation I added more ether and allowed the solution to stand ten days longer. At the end of this time I collected the crystals on a hardened filter, washed them carefully with alcohol-ether, dissolved them in a little water and recrystallized them from solution by the addition of alcohol and ether. The quantity obtained was minimal and not sufficient for analysis. I dissolved the crystals, therefore, in very little distilled water and tested them for pharmacological action.

EXPERIMENT 3. Nov. 1, 1907. Rabbit (2 kg.) receives, 11 A.M., 1 ccm. solution of colorless crystals intravenously. Animal at first normal except for slight restlessness. 1 P.M., animal somnolent, purging and passing of urine. 1.30 P.M., somnolence increases; animal crouches in corner with eyes closed and does not react to loud noise; slight reaction to tactile stimuli;

animal very easily hypnotized in every conceivable position, and difficult to rouse from hypnosis. Respirations 136, labored. Marked tremor from time to time; pronounced trismus. The animal's snout appears peculiarly pointed on account of muscular contraction. 3.30 P.M., stupor constantly deepening. When placed flat on its back the animal remains for hours in this, for it, most uncomfortable position. Concussion of the substratum produces violent trembling, but does not rouse the animal from the hypnosis. Frequently repeated concussions cause the animal slowly to rouse from his stupor. Respiration, 192. Temperature, 105°. Veins of ears strongly injected.

Nov. 2. Animal apparently recovered.

Nov. 10. Animal found dead.

The foregoing experimental investigation would seem to show that there are certain cases of acute intoxication, due to a definite non-proteid active principle, which during life present the clinical picture of eclampsia. Much more experimental work will be necessary to enable us clinically to distinguish the cases in which the toxin is present, from cases of "eclampsia" due to other causes, such as epilepsy and uremia. The solutions I obtained do not as a rule produce the convulsions typical of eclampsia. Possibly the toxic substance undergoes certain modifications of structure or composition during its isolation which affect the quality of its action. Of recent years numerous cases of "eclampsia without convulsions" have been described; perhaps the toxin acting in these cases is identical with the substance obtained by me. In order to pro-

duce its action the toxin and solutions containing it must be given intravenously. This is true of many other poisons. Possibly the toxin is rendered inactive by combination with a tissue-component when it is given subcutaneously.

As to the pharmacological character of the toxin little can at present be said. It seems to act as a protoplasmic poison. It paralyzes the centers of the brain and cord, especially the respiratory center.

I have at present material in hand which may make it possible for me to obtain a sufficient amount of the toxin for analysis and chemical characterization.

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THE TENT WARD AT THE MASSACHUSETTS GENERAL HOSPITAL.

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AT the present time, when hospital construction is thought of as being accompanied by great expense, it may be of interest to know how much can be accomplished with a comparatively small outlay.

During the spring of 1907, two wards at the Massachusetts General Hospital were to be renovated at once. One ward was moved to the "Relief Ward," the other to the "Tent Ward." This ward was open from June 13 to Nov. 1.

The Tent Ward was equipped as follows: there were two tents, 14½ x 19½ feet in dimensions, each of which could accommodate three patients easily, and four if necessary; one tent, 14½ x17 feet, used as a kitchen and fitted up with ice-box, electric-toaster, water-cooler, sink and tables; eight tents, 12 x 17 feet, six of which were used for patients, two being accommodated in each tent, so that a total of eighteen patients could be accommodated; one of the two remaining tents was fitted up with medicine closets, chests for linen and blankets, and a table and chairs for nurses' use; and in the other there were a bath-tub, hop-

per, toilet, sink, and rack for solutions. The tent last mentioned and the kitchen tent had hot and cold water and sewer connections. All tents were provided with a fly and the walls could be rolled up for better ventilation. Ventilation was also aided by slits in the roof of tents, protected by the fly. The lighting was by electricity, and in each tent there was a Hy-lo electric lamp so attached as to be portable to all parts of the tent. The tents were arranged in a long row with the two large tents at the ends and with the medicine and solution tents in the center of the row; the kitchen tent was opposite and at a short distance from the center of the row. In front of one of the large tents a fly was spread of the same size as the tent and used as an office; it was equipped with desk, chairs, telephone and couch. All tents had a flooring of $\frac{7}{8}$ in. spruce, laid on 2 x 3 joists, and there were walks of the same material connecting them. The beds were " dormitory beds " with low head, with " National wire springs " and one mattress. There were a table and chair for each bed. In the latter part of the season each bed was supplied with two mattresses, extra blankets, and when necessary hot-water bottles and soapstones were used, and even when the weather became quite cold, a tent could be warmed in fifteen minutes by means of an oil heater, so that baths could be given. Hot air baths were given with good results until the weather became quite cold. The total actual outlay for the tents, which were sec-

ond hand, for lumber, labor and lighting was $525. Everything else came from the general supplies of the hospital. All food came from the hospital diet kitchen.

Three nurses and one head nurse were assigned to the ward. The work was not more difficult than the regular ward work, the increased distances and the difficulty of watching all the patients being compensated for by the greatly diminished housekeeping necessary. There were two night nurses, for the double purpose of watching the patients sufficiently and to avoid loneliness. Canvas hats were worn by the nurses as a protection against sun and rain, and rubber coats and boots in stormy weather. The nurses, without exception, enjoyed the work, none was in any way harmed by exposure, and the general health of all seemed improved, in some cases quite markedly.

Ninety patients were admitted to the tent ward. There was no selection of cases until the last two weeks when, because of the inclement weather, it seemed wise to admit to the ward only patients whose condition called for out-of-door treatment. The mortality was seven, none in any way due to the open air treatment; two were cases of pernicious anemia who died shortly after admission and both of whom had been admitted to the hospital several times previously; two were suffering from chronic interstitial nephritis with uremia; one died on the day of admission, the other responded to treatment well at first, but died at the end of a week. One fatal

case was a patient with cardiac disease who died shortly after admission; another cardiac case with embolism died after two weeks' stay in the ward, and the last (the seventh) was a patient who had severe myocarditis. The cases of typhoid, twelve in number, all made good recoveries; though several of them were very sick and five had relapses; they seemed to require fewer baths than one would expect in a closed ward. Patients with pleurisy with effusion and tubercular peritonitis, excepting two which were very far advanced, patients with pneumonia, bronchitis, debility and neurasthenia, as would be expected, did remarkably well.

Cases of arthritis were watched with interest, but there were no cases where the course of the disease seemed to be prolonged by the fresh air treatment. The renal and cardiac cases seemed to be benefited by being out-of-doors. Three cases of malaria were admitted and were segregated only by individual mosquito nets, but no case of malaria developed in the ward.

Perhaps the most remarkable clinical fact was the great reduction in the frequency with which hypnotics had to be prescribed, even in the cases where the patients were high-strung, and even the pain due to malignant disease seemed to be controlled by much smaller amounts of analgesics than would ordinarily be expected.

However, the most striking feature was that the patients, all women, and all belonging to the humbler classes, really the most conservative por-

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tion of society and with whom fads and innovations find the least favor, in all cases took kindly to life in the open, and after a short experience with tent life enjoyed it immensely and seemed to consider it a hardship when, for any reason, they had to be transferred to a regular ward.

I wish to express my thanks to Dr. Herman F. Vickery, visiting physician to the Tent Ward, for whom the writer was senior house-officer during the greater part of the existence of that ward, at whose suggestion this account is written, and to Dr. Frederic A. Washburn, acting administrator of the Massachusetts General Hospital, for permission to do so.

THE HISTOLOGY OF MULTIPLE MYELOMA. A COMPARATIVE STUDY OF ELEVEN CASES.*

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(From the Laboratory of the Department of the Theory and Practice of Physic, Harvard University.)

SINCE Bence Jones, in 1848, studied the peculiar proteid body excreted in the urine of a patient with diseased bones, an increasing number of cases have appeared in the literature, and gradually this urinary condition has come to be regarded as almost pathognomonic of certain bone tumors, myelomata. The chemical constitution of the Bence Jones body, however, still remains uncertain, notwithstanding much study of this phase of the subject. The reason for its formation and excretion, when such tumors occupy the bones, is practically unknown. The symptomatology and pathological anatomy on the other hand have been very thoroughly studied, for now the reported cases are quite numerous. The pathological histology of multiple myeloma, however, like its chemistry, has remained a matter of discussion, and more particularly with regard to the cytology of the condition is this true. Finer details of cell structure could not be studied in

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the earlier cases as they were investigated at a time prior to the development of the modern histological technic. In the reports of recent cases differences of opinion as to the nature of the tumor cells have arisen, either because actually tumors of different cell structure have been included under the term myeloma or because too few cases have been examined by one investigator for the range of possible variation in tumor cells histogenetically the same to be appreciated. Three cases seem to be the largest number carefully studied by one individual previous to my reports in 1907.[1] Since then, through the courtesy of friends, I have been able to collect five more cases, making a total of eleven cases available for comparative histological study.

Since the important factor in determining the nature of the cells in multiple myeloma is a comparison, side by side, of sections from different cases, a brief summary of the histological appearances of the six cases previously reported will be given, accompanied by photomicrographs, and the histological description of the new cases will be given in greater detail. It will be possible then to summarize the histology of myeloma as illustrated by this group of cases and to show by means of the photomicrographs taken under similar conditions of preparation and magnification that there is a marked similarity in the cells of all cases, but that there are minor variations

[1] Christian: Multiple myeloma: A histological comparison of six cases. Jour. of Exp. Med., 1907, ix, 325.

in detail of structure which is not so great but that the tumors may be arranged in series so that between the individual cases of the series the differences are exceedingly slight.

CASE I.[2] Sections[3] show the tumor to be very cellular and to consist of cells varying only moderately in size, shape and structure. (Fig. 1.) The cells lie in a coarse-meshed reticulum. The individual cells are round, oval, roughly polygonal or cuboidal. (Fig. 13.) There is no cell membrane. Not infrequently the cell edge is slightly ragged. The cytoplasm is slightly basophilic and is finely granular. The nuclei of most of the cells are round or oval, with a distinct nuclear membrane. The nuclei are vesicular and have a fine chromatin net-work with coarser chromatin masses attached to the nuclear membrane and scattered throughout the central part of the nucleus. The nuclei contain a distinct metachromatic nucleolus. Slight variations from this cell structure occur, but they are not very common.

CASE II. This tumor is made up almost entirely of cells. (Fig. 2.) Connective tissue reticulum is very slight in amount. The cells vary somewhat in shape, but usually they are rather polygonal. (Fig. 18.) There is no cell membrane. The cytoplasm has a very finely granular ground-glass appearance. Some cells are finely vacuolated and may have a ragged outline. The cytoplasm is slightly basophilic. The nuclei are round, sometimes oval, sometimes slightly irregular in contour. The nuclei are almost always

[2] For further details in regard to cases I–VI, see Jour. Exp. Med., 1907. ix, 325–343. Here also will be found an acknowledgment of the sources of the material in each case and a statement as to whether it has been described elsewhere.

[3] Unless otherwise noted, all tissue was fixed in Zenker's fluid.

eccentrically placed in the cell. There is a distinct nuclear membrane. Chromatin masses are small and tend to a peripheral position against the nuclear membrane. A distinct metachromatic nucleolus is common. The nuclei in this tumor show considerable variation in structure, but the one described above is the most common type.

CASE III. This is a very cellular tumor with a fine meshed reticulum. (Fig. 3.) The cells are round, slightly oval, sometimes polygonal. (Fig. 12.) Cell outline is distinct and regular, and in places there is some indication of a cell membrane. The cytoplasm is very finely granular or almost homogeneous and is very slightly basophilic. Nuclei are round or oval, usually of regular contour. In relation to cell body the nucleus is rather large. It usually has an eccentric position. There is a distinct nuclear membrane. The nuclei are vesicular with rather fine chromatin masses diffusely scattered. At times there is a slight peripheral grouping of the chromatin, but this is never very marked. Many nuclei show a metachromatic nucleolus.

CASE IV is a cellular tumor with sparse stroma of reticular type. (Fig. 4.) The cells are oval to roughly polygonal and have a distinct cell outline. (Fig. 22.) In some sections the nuclei are distinctly eccentric in the cell. Cytoplasm is finely granular, almost homogeneous. Some of the cells show a ragged, frayed-out edge. Cytoplasm is weakly basophilic. Nuclei are vesicular, with a distinct membrane. Chromatin is present in rather small masses scattered throughout the nucleus. There is a slight tendency to peripheral grouping of the chromatin. Many of the nuclei contain a metachromatic nucleolus.

CASE V. In some parts of this tumor connective

tissue stroma is present in large amount, and everywhere it is more abundant than in the preceding tumors. (Fig. 5.) Tumor cells here vary more in shape than in the other cases because they frequently appear to be crowded into narrow crevices between connective tissue bundles. Where this is not the case they are oval or polygonal. (Fig. 16.) The cell outline is sharp though there is no indication of a cell membrane. Cytoplasm is homogeneous, very finely granular, at times it is finely vacuolated. Cytoplasm is weakly basophilic. Nuclei are round or oval, sometimes slightly irregular, almost always eccentric in the cell. Chromatin is in fairly fine masses scattered throughout the nucleus, but is relatively not very abundant. There is a slight tendency to peripheral arrangement of chromatin masses. In many nuclei there is a metachromatic nucleolus.

CASE VI. Stroma is very slight in amount in this tumor, and appears as a delicate, coarse-meshed reticulum. (Fig. 6.) The tumor cells are of a surprisingly uniform appearance. They are round or oval, frequently polygonal. (Fig. 23.) The cytoplasm is almost homogeneous and has a slight affinity for basic dyes. The nucleus is almost always round and an eccentric position is almost constant. Chromatin masses are relatively large in size, and for the most part lie in close apposition to the cell membrane so that there is left a small central portion rather free from chromatin. In a moderate number of the cells there is a distinct metachromatic nucleolus.

CASE VII (University of Buffalo, 2368) [4] was autopsied by Dr. C. A. Bentz, of Buffalo, on Oct. 13, 1904. This was a patient, a male, aged forty-nine years, who

[4] I take pleasure in expressing here my thanks to Dr. Bentz for his courtesy in furnishing this tissue and his permission to use it in this connection.

had been in good health almost up to the time of his admission to the hospital on July 5, 1904. Three months prior to this time he began to feel severe pain along the course of the sciatic nerves. Previously he had had occasional twinges of pain in the same region. The pain during the three months had grown steadily worse and the patient was confined to bed almost all of the time. The urine examination showed a few hyaline casts and albumin, but no mention is made of the presence of albumose. The autopsy showed cirrhosis of the liver and chronic interstitial nephritis. There were osseous projections laterally from the bodies of the vertebræ and a tumor growth in the sternum and third lumbar vertebra. The tissue from these tumors preserved in formalin was put at my disposal for study.

The tumor is for the most part very cellular, with a small amount of intervening stroma. (Fig. 7.) In other places the cells are separated by a fair amount of connective tissue. Throughout the tumor there are numerous blood vessels of relatively large caliber and thin walls. Many sections show an extensive degree of hemorrhage into the cellular portions of the tumor; this is so marked in places that it gives the appearance of a blood clot, with here and there scattered small groups of tumor cells.

The tumor cells themselves are of a quite uniform appearance, not varying very greatly either in size, in shape or in staining reaction. The contour of the individual cells (Fig. 19) is regular and sharply outlined, but there is no evidence of a distinct cell membrane. The cells are for the most part round or slightly oval. Where they are most crowded together there is a slight tendency to a polygonal shape, and in a few places where stroma is fairly abundant the cells may be squeezed into somewhat irregular shapes. The

average of a number of measurements of these cells is 9 x 7.7 microns. The cytoplasm of the cells, whether stained with hematoxylin and eosin or with phosphotungstic acid hematoxylin after mordanting with picric acid and ammonium bichromate, is very homogeneous, presenting a ground-glass appearance (Fig. 19), with only an occasional cell that is finely vacuolated. The cytoplasm is distinctly, though moderately, basophilic. The cells in this tumor do not show the ragged, frayed-out edge due to peripheral vacuolization as described in some of the other of these tumors.

In the phosphotungstic acid hematoxylin preparations many of the cells show near the nucleus a distinctly paler zone, near whose center lie two minute dots similar to those described in the preceding tumors and considered to be centrosomes. These dots lie very close together and frequently it is impossible to make out more than one dot. This appearance of a single dot may be due either to the fact that one dot overlies the other dot or to the fact that it is not always possible optically to resolve bodies lying as close together as some of these may.

The nucleus of these cells usually has a distinctly eccentric position in the cell body, and frequently it lies peripherally. (Fig. 19.) The nuclei themselves are round or oval and the average of a number of measurements is 5.3 x 4.6 microns. Occasionally a nucleus has a slightly irregular contour or it may show an indentation of its sides suggesting direct division. Sometimes a nucleus has a pseudopodic projection, but this is not common. Nuclei vary rather more in size than do the cell bodies, still there is no very great irregularity in nuclear structure. The chromatin is present in rather fine masses which show a slight tendency to a peripheral grouping. (Fig. 19.) How-

ever, this is not marked and there is no definite mural arrangement of the chromatin, though there appears to be a fairly distinct nuclear membrane.

A number of cells show near the center of their nucleus a small, rounded mass tending to stain slightly metachromatically and which may be regarded as a nucleolus. Here again this is not a very marked feature of the tumor, though in some of the cells the mass is very distinct. No mitoses were found in the examination of a large number of fields.

Three variations of the type cell of the tumor occur, but the total number of these cells is very small. Some of the cells have two, three or rarely four, nuclei, with a corresponding increase in the size of the cell body. Other cells have nuclei larger, more deeply staining and slightly more irregular in contour than the type cell. The upper limit of the size of these nuclei is about 2½ times the average nucleus. A moderate number of cells have nuclei which show slight degrees of shrinkage with a diffuse, rather dark staining nucleus (pyknosis). There is no evidence of hemoglobin staining in the tumor cells even where there is marked hemorrhage, and in this respect the tumor differs from most of the preceding ones.

Case VIII (Myeloma "X").[5] Tissue consists of a portion of a rib and part of a nodule adjacent to the rib. Both pieces were preserved in alcohol. There is no bone present in the nodule, whereas tissue from the rib contains bone requiring decalcification with 5% nitric acid before sectioning. This is a cellular tumor with rather more fibrous tissue stroma than was present in many of the other specimens of myeloma. Again, the arrangement of the stroma is rather different from

[5] For this tissue I am indebted to Dr. E. Libman, Mt. Sinai Hospital, New York, to whom I express my thanks. This patient did not come to autopsy.

most of the other cases in that there are moderately coarse connective tissue bundles forming elongated spaces or meshes in which the cells are closely crowded, with little or no intercellular stroma. (Fig. 8.) Blood vessels for the most part run in these connective tissue bundles and consequently have fairly definite, rather thick walls in comparison with the diameter of the blood vessels themselves. Individual cells vary considerably in shape, depending upon how closely crowded together they are. Where they lie fairly far apart they are for the most part of an irregular, oval shape; sometimes they are round, but more usually they are polygonal, owing to pressure of adjacent cells, but even under these conditions they are very apt to have one diameter longer than the other. (Figs. 14 and 15.) They are of a fairly uniform size, and the average of a number of measurements is 11.2 x 10 microns. The cell outline is almost always distinct, but there is no suggestion of a cell membrane. The cytoplasm is finely granular, of a ground-glass appearance (Fig. 27), but some cells have a slightly more coarsely granular cytoplasm. Occasionally a cell is finely vacuolated. (Fig. 14.) The latter, however, is an infrequent finding and is not sufficient to give the cells the frayed-out ragged border which has been described in several of the other cases. The cytoplasm is distinctly, though not markedly, basophilic. The nucleus very frequently is eccentrically situated, and it is unusual to see the nucleus distinctly centrally placed. (Figs. 14, 15 and 27.)

The nuclei are round to slightly oval and have a distinct outline which may be interpreted as a nuclear membrane. (Fig. 14.) The nuclei vary considerably in size and also in structure. Some of them are distinctly vesicular with fine chromatin granules which

show a distinct tendency to group themselves peripherally on the nuclear membrane. In others there is very little peripheral grouping of the chromatin. In most of these nuclei, usually somewhat eccentrically placed, though sometimes in the center, there is a distinct, rounded, homogeneous, refractile mass, staining with eosin and averaging 1 micron in diameter, rarely 2 microns. (Fig. 15.) This is interpreted to be a nucleolus. Nuclei of this type average 6.6 x 6.1 microns in diameter.

Another very common type of nucleus is about one half the size of the one previously described, is very much less vesicular, the chromatin granules are coarser or more or less fused together into a diffusely staining mass. This type of nucleus seems to pass by gradual transitions into one still smaller, more homogeneous and more deeply staining, until finally the nucleus is represented by a deeply stained, homogeneous mass, one quarter or less the size of the first described vesicular nucleus. It would seem that this represents a progressive, degenerative change with shrinkage of the nucleus from the original vesicular nucleus. Another very common type of cell has a nucleus no longer vesicular and in which the nuclear material forms itself into six to ten rounded homogeneous, deeply-staining masses varying in size from one to two microns. (Fig. 27.) In a number of these cells the masses group themselves peripherally, and the nucleolus can still be distinguished in the center. However, the nuclear membrane often seems to have disappeared or to be only indefinitely represented. (Fig. 27.) Instead of a nuclear membrane, very frequently there is a pale zone immediately around the nuclear mass, as if this nuclear material lay in a vacuole; and with the peripheral grouping of the globules of nuclear material it frequently pre-

sents a picture not dissimilar from that shown in certain stages of the segmentation of malarial parasites.

In other cells, with the disappearance of the nuclear membrane, the chromatin masses appear to lie free in the cytoplasm of the cells. In this type of cells the nuclear masses may remain connected to each other by means of a fine thread staining indistinctly with nuclear stains. In some fields of the sections this type of fragmented nucleus is much more abundant than in other fields, though there is no other difference suggestive of a cause for this.

An occasional cell contains two or three nuclei, and in the latter the nuclei may show any of the varieties of structure already described. No positive evidence of mitosis can be found in the cells of this part of the tumor. Sometimes the formation of separate nuclear fragments gives a picture suggestive of some stage of mitosis, but in all cases it seemed that the picture could not justly be interpreted as one of mitosis. These changes are regarded rather as a peculiar form of degeneration, such as has already been described in some of the previous cases. Moreover, there is no indication of indirect division taking place in the cells.

The sections made from portions of the rib and adjacent tissue after decalcification show almost complete disappearance of the marrow and replacement by tumor tissue. Here the tumor does not show the arrangement with coarser bands of connective tissue enclosing groups of tumor cells, but there is a rather more generally distributed connective tissue framework made up of very delicate connective tissue bundles and thin walled, small blood vessels which frequently lie in close apposition to tumor cells. Fragmentation of the nucleus and formation of several small masses of nuclear material do not appear to take place except infre-

quently in these portions of the tumor. The tumor cells in these sections, however, have the same general characteristics with regard to cytoplasm as described above. Numerous shrunken, more deeply staining nuclei occur as in the adjacent nodule. Mitotic figures occur and are not very infrequent in these sections. The trabeculæ of bone seem to have atrophied to a great extent; the tumor has penetrated the bone in places and infiltrated the adjacent fibrous, adipose and muscular tissue. The distinctly invasive character of the tumor growth is best shown where the tumor has invaded striated muscle and the tumor cells are crowded between the muscle fibers. In a few of the sections the bone marrow is not entirely replaced by the tumor, and tumor cells can be seen scattered singly or in small groups amidst the bone marrow cells. The tumor cells can be easily picked out from the other marrow cells by their larger size, the distinct nucleolus and the fine chromatin granules tending to group themselves on the periphery. No hemoglobin pigmentation of the cells in this tumor can be made out.

Case IX (Buffalo Myeloma, No. 2).[6] This case, a man of forty-nine years, was autopsied Oct. 11, 1907, by Dr. C. A. Bentz, in Buffalo. There were numerous tumors present in the bones of the skull, clavicle, ribs and sternum. The eighth rib on the left side showed a growth the size of an English walnut, which had produced fracture of that bone. The fifth rib on the right side showed a similar tumor. At the junction of the gladiolus and manubrium sterni there was a tumor mass about the size of a dollar, and here the bone also was fractured. At the sterno-clavicular articulation on the right side there is a growth 2½ in. long and 2 in. in

[6] This case was placed at my disposal by Dr. C. A. Bentz, of Buffalo.

width, which originates in the clavicle and presents on section a mottled gray and red appearance. This bone, too, is fractured. Above the left ear in the skull there is a mass the size of a silver dollar which is soft, with crater-like edges. On the forehead, 3 in. above the right eyebrow, there is a similar mass the size of a hazelnut, and another back of the right ear. The abdominal and thoracic viscera present no abnormalities, and there is no evidence of any metastases beyond the bones.

This tumor is composed almost entirely of cells, among which there are scattered a few connective tissue fibrils forming an ill-defined reticular meshwork. (Fig. 9.) In addition there is a moderate amount of connective tissue accompanying rather large blood vessels, but the walls of the blood vessels for the most part are thin. In some sections, however, there are very large blood vessels with quite thick connective tissue walls containing relatively few cells and no definite muscularis or elastic tissue layer. These areas give the appearance of an angioma made up of rather large venous sinuses, between the walls of which are scattered the myelomatous tumor. Hemorrhagic areas occur quite often.

The cells in this tumor are of quite uniform size. For the most part the cell outline is distinct without there being anything to suggest a cell membrane. (Fig. 21.) The cytoplasm is almost homogeneous or finely granular and has a distinct affinity for basic stains. Some cells show a fine vacuolization of the cytoplasm. The average of a number of measurements is 10.2 x 8.7 microns.

The nuclei most usually have an eccentric position in the cells (Fig. 21), though the cells in proportion to the size of the nucleus are frequently not very large and often one diameter is not very much greater than the

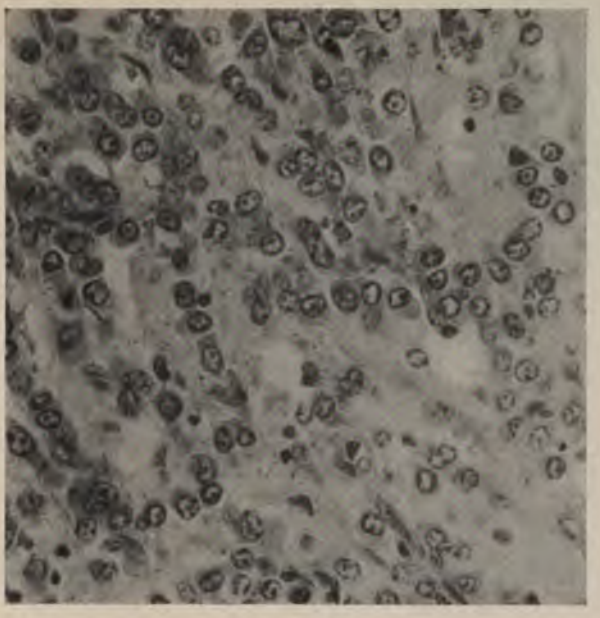


FIG. 1. CASE I.

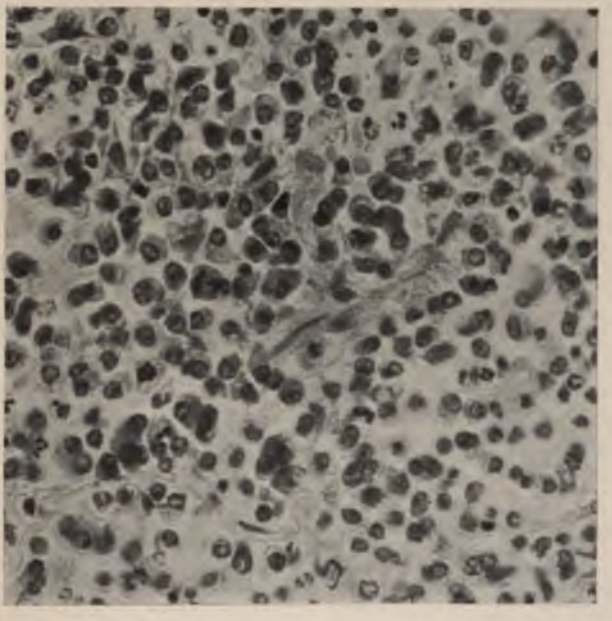


FIG. 2. CASE II.

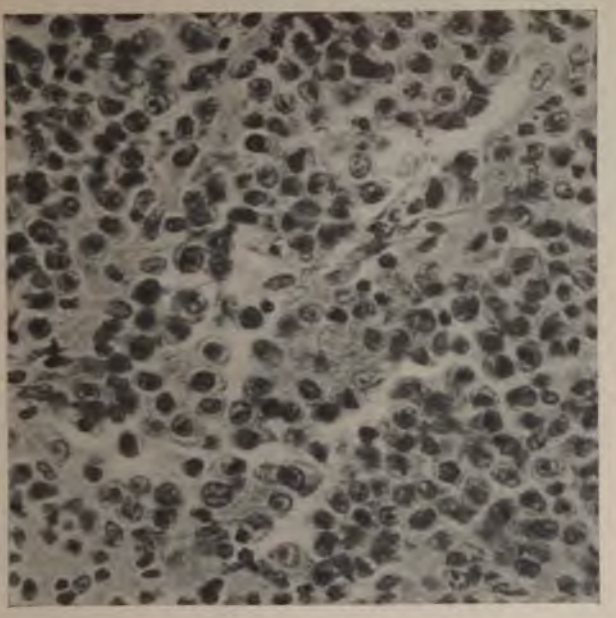


Fig. 3. Case III.

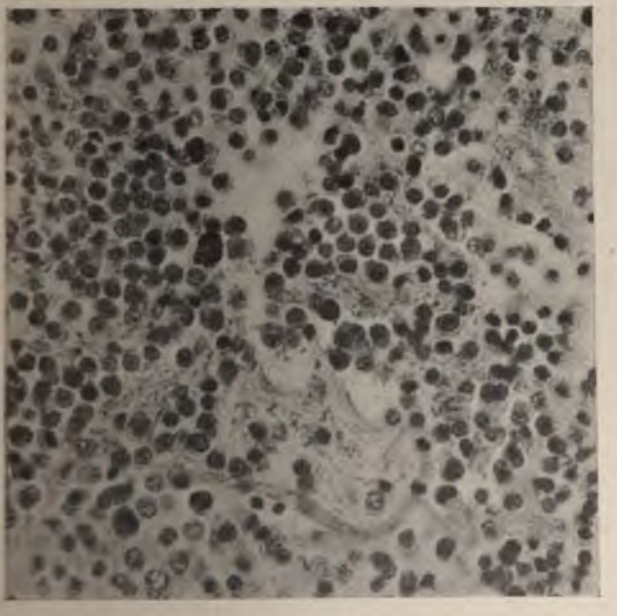


Fig. 4. Case IV.

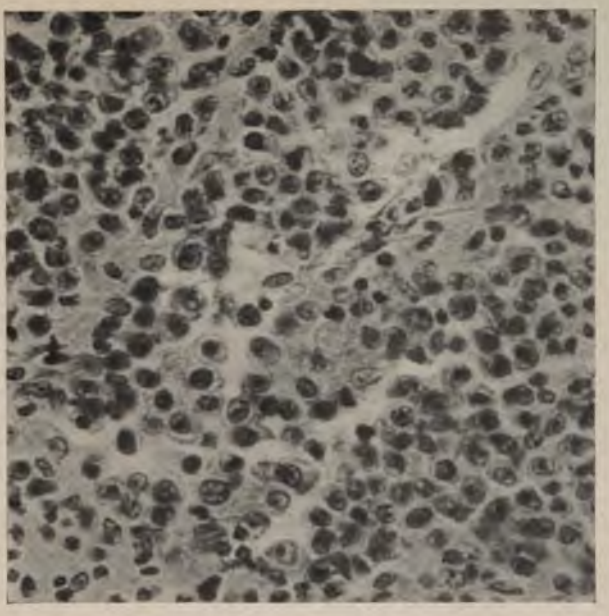


Fig. 3. Case III.

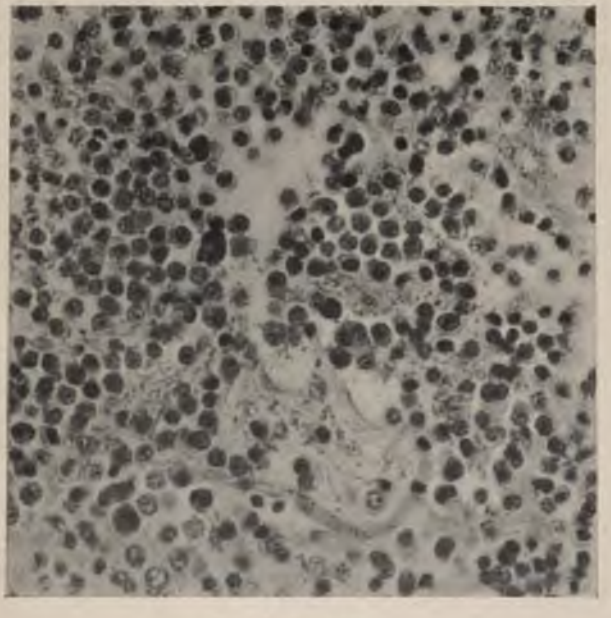


Fig. 4. Case IV.

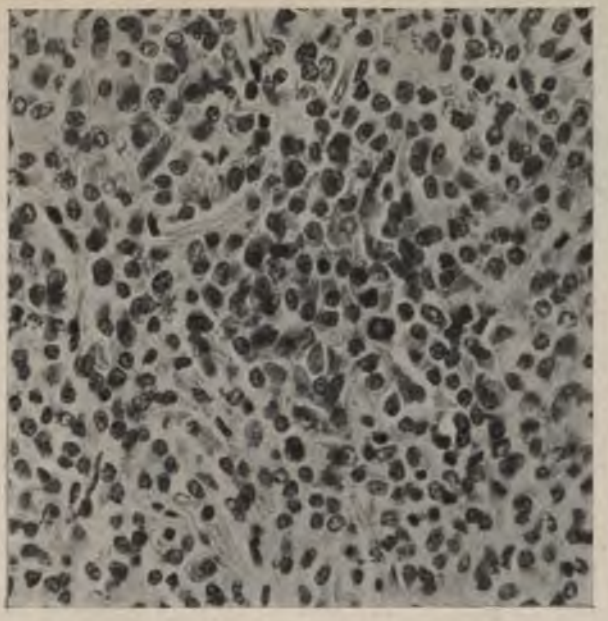


Fig. 5. Case V.

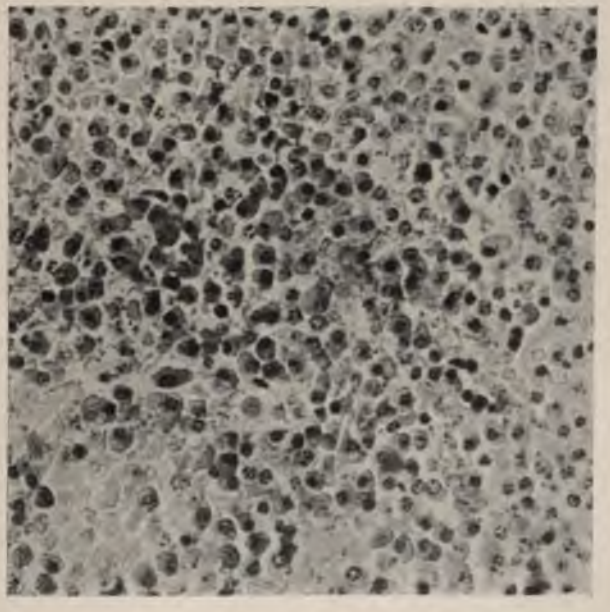


Fig. 6. Case VI.

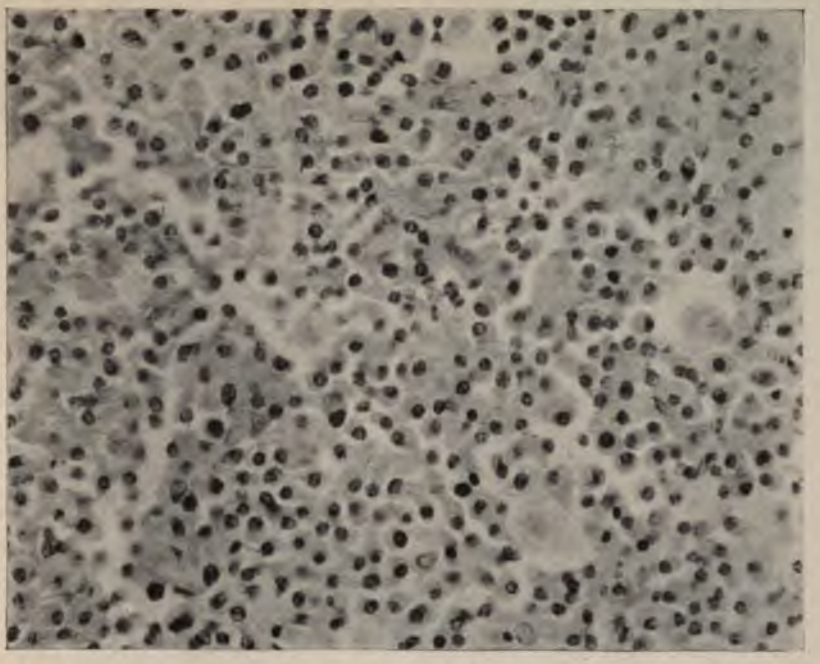


FIG. 7. CASE VII.

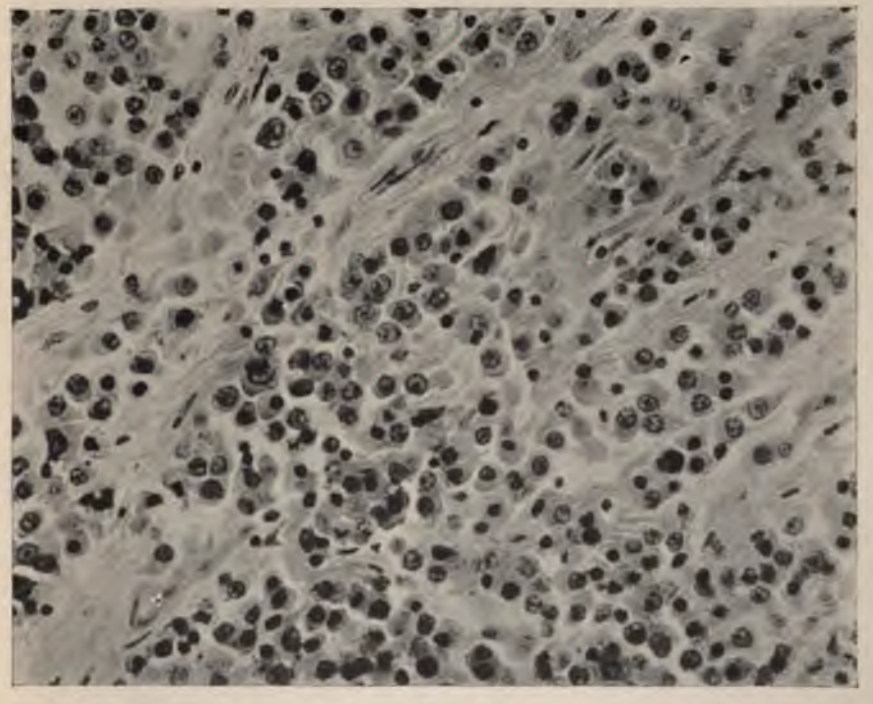


FIG. 8. CASE VIII.

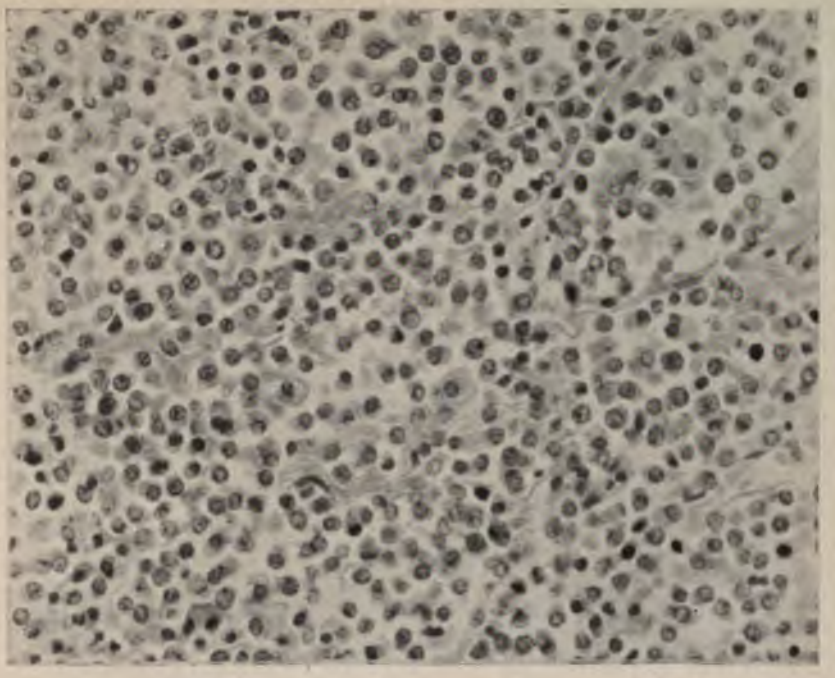


Fig. 9. Case IX.

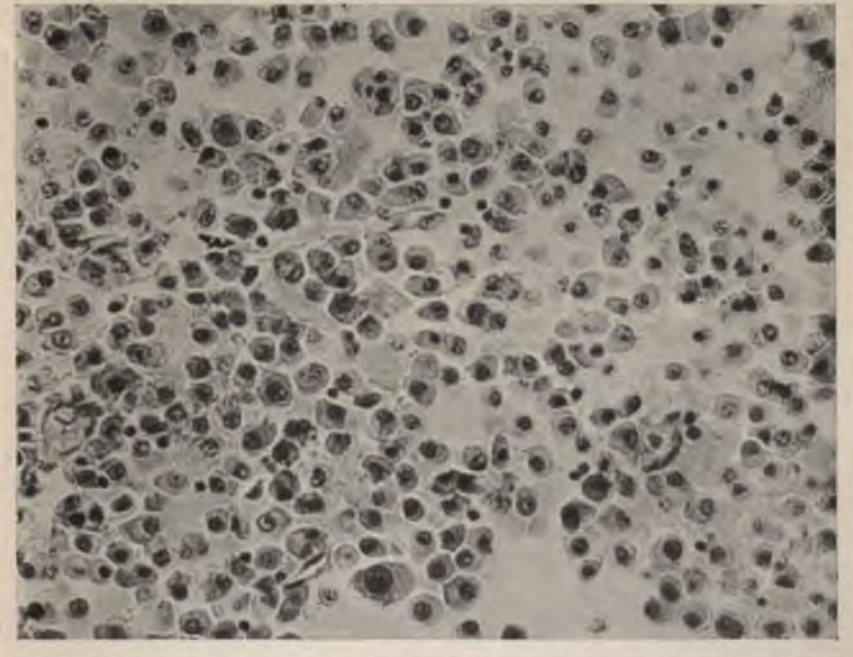


Fig. 10. Case X.

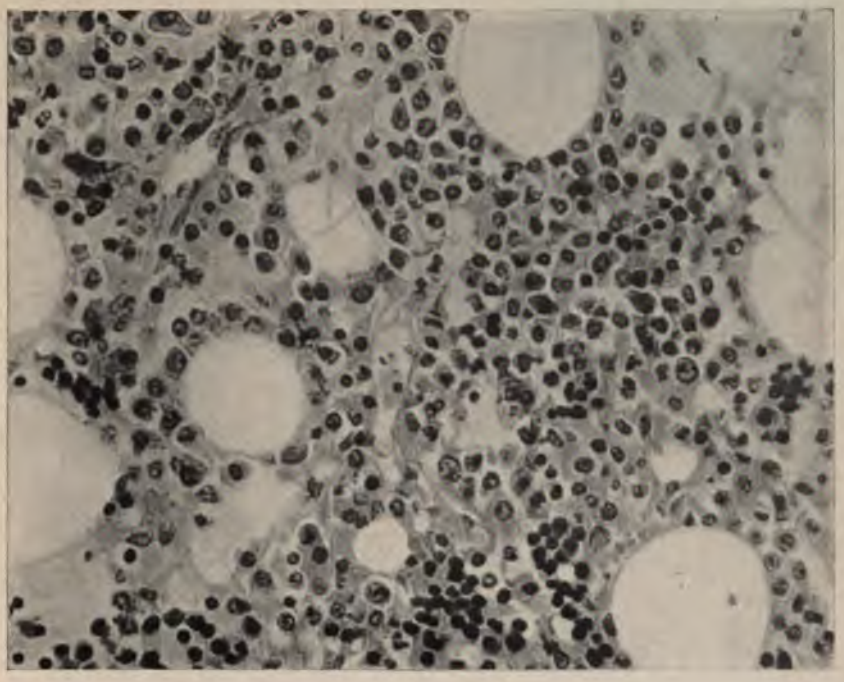


FIG. 11. CASE XI

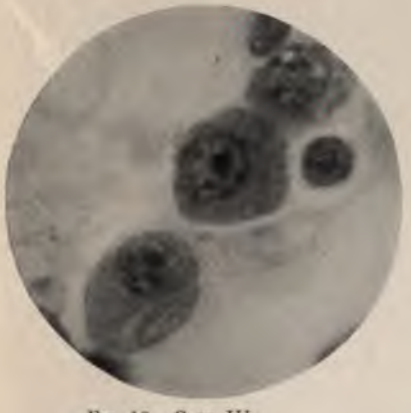


FIG. 12. CASE III.

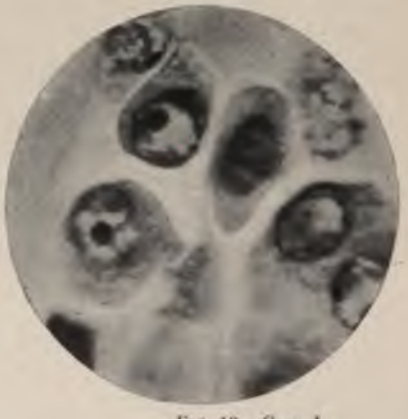


FIG. 13. CASE I.

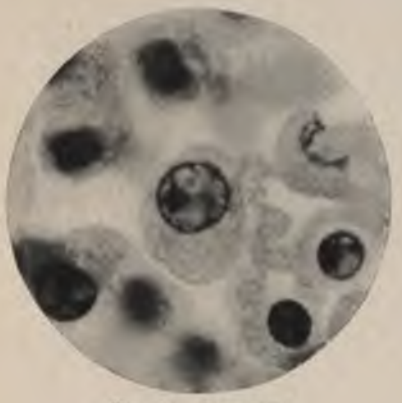


Fig. 14. Case VIII.

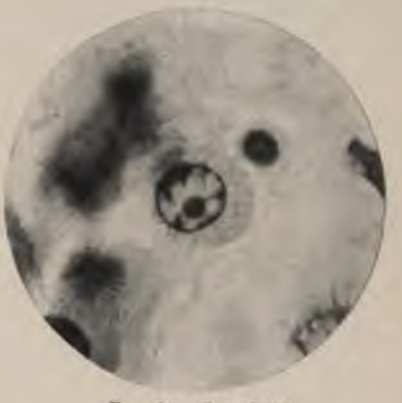
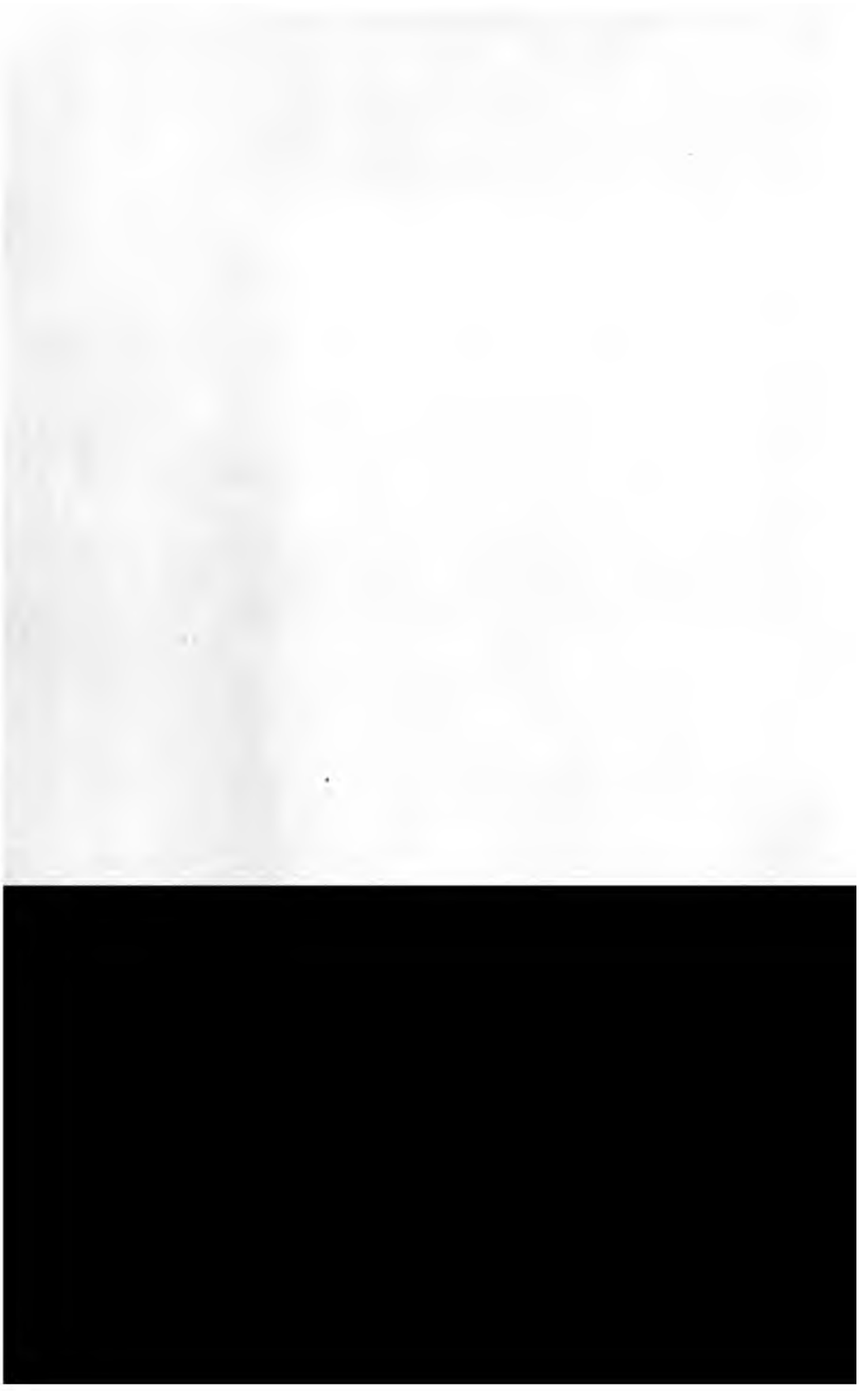


Fig. 15. Case VIII.

Fig. 16. Case V.



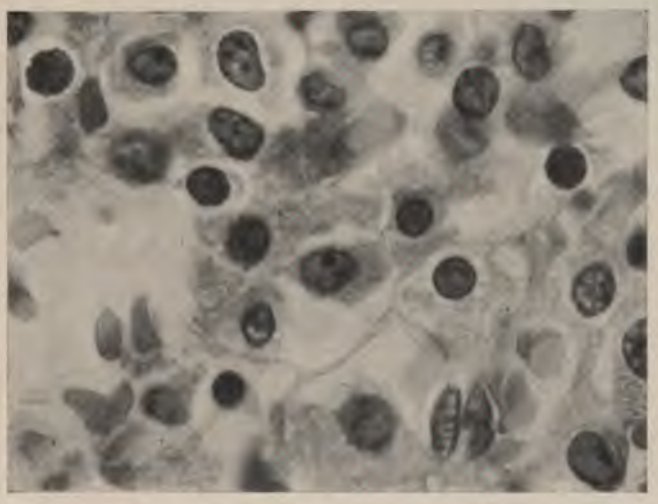


FIG. 17. CASE XI.

FIG. 18. CASE II.

FIG. 19. CASE VII.

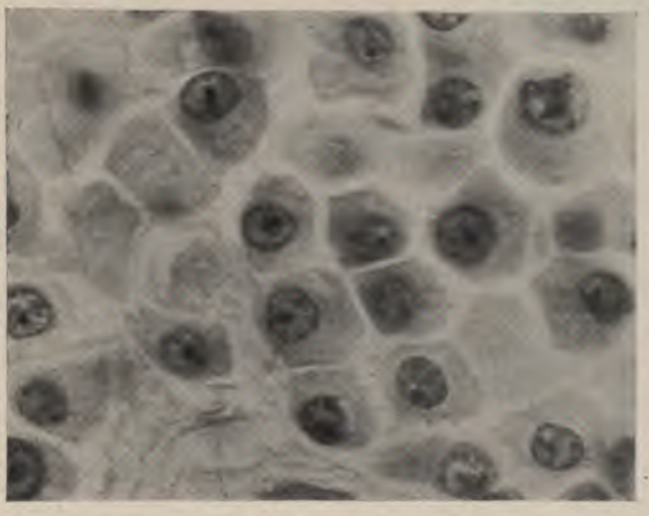


FIG. 20. CASE X.

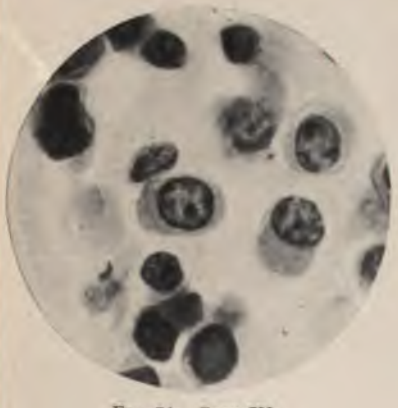


FIG. 21. CASE XI.

FIG. 22. CASE IV.

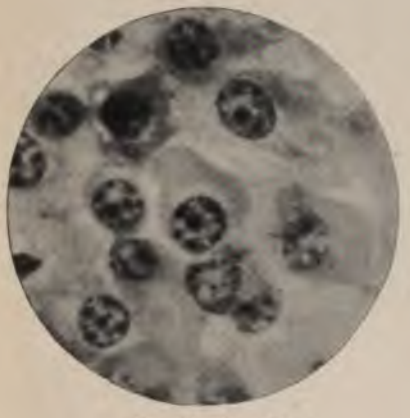


FIG. 23. CASE VI.

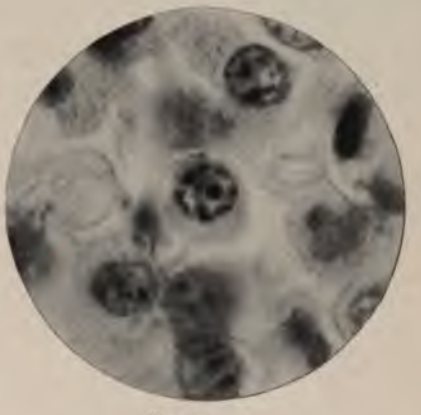


FIG. 24.

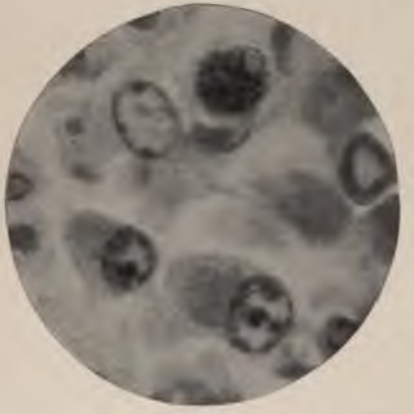
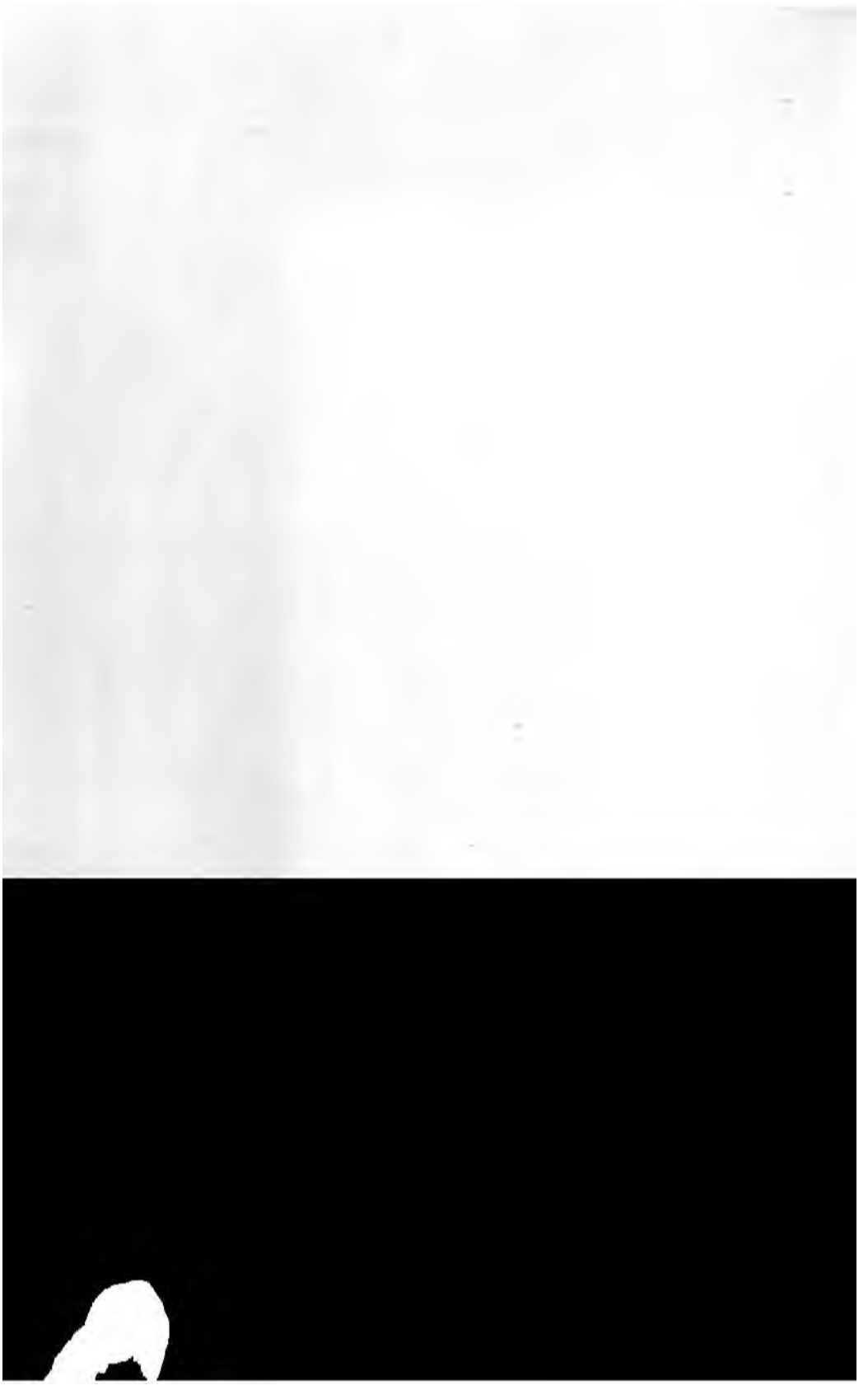


FIG. 25.



other. Consequently, many of the cells show only a moderate rim of cytoplasm about the nucleus, and in such cells very marked eccentricity of position cannot take place. The typical nucleus is vesicular, with a distinct nuclear membrane, on which is clustered fine chromatin granules so as to give the nucleus a distinct, rather deeply staining, periphery, while scattered through the center there are rather few fine and occasionally coarser chromatin granules. (Fig. 21.) Quite a number of the nuclei show a distinct, rounded acidophilic, homogeneous body, the nucleolus. (Fig. 21.) These nuclei average 6.9 x 6.1 microns in diameter. Numerous cells are distinctly larger than these just described, and in them the nucleus is proportionately larger and has rather coarser chromatin granules without showing any other difference of structure. Some of these larger cells have two to five nuclei, though the multinuclear cells are not a predominating feature of the picture. Mitotic figures are easily found in cells of the types just described.

A common variation from cells just mentioned appears to arise from a gradual shrinkage of the nucleus, in which the nucleus as it shrinks becomes more compact and deeply staining, until it is finally represented by a shrunken, homogeneous, deeply staining mass. With the shrinkage of the nucleus there appears also to be a shrinkage of the cytoplasm, which also becomes denser and more homogeneous. The cells of the type just described very frequently show hemoglobin staining of their cytoplasm, and not infrequently they are as deeply stained with hemoglobin as are the red blood corpuscles. This phenomenon is observed most markedly in those areas in which there are scattered many free red blood corpuscles and in the vicinity of thin walled blood vessels and definite areas of hemor-

rhage. Here and there a nucleus presents the appearance described in the preceding tumor, in which the nuclear material becomes aggregated into several small globules. These cells are not infrequently stained with hemoglobin and resemble closely the nuclei of certain megaloblasts in pernicious anemia, in which I have frequently noted similar changes in the chromatin.

Scattered between the cells in many areas of the tumor are many hyaline, slightly eosin staining or sometimes slightly basophilic, homogeneous droplets, which measure one to two microns in diameter. Here and there an eosinophilic leucocyte has been noted in the tumor, and also a few cells indistinguishable from the plasma cells of the connective tissue. In places there appear to be intermediate stages between cells identified as plasma cells and the tumor, and it is possible that these plasma cells have arisen from tumor cells which, after all, do not differ very markedly from plasma cells except that they are larger and the usual characteristics of plasma cells are less well marked. Probably the most striking thing in regard to this tumor, as in so many of the others, is the very uniform appearance presented by any field of the tumor and the slight variation in the appearance of the cells that predominate in the tumor, notwithstanding the variations in structure which have already been described.

Here and there are quite large phagocytic cells with included cells and cell fragments. The nucleus of these phagocytic cells, when it can be made out, is distinctly more vesicular and paler than the tumor cells, is apt to be elongated or irregular in contour and resembles the nucleus of the typical phagocytic endothelial type of cell. It is very probable that these cells are endothelial cells associated with the reticular framework of the

tumor, as is so common in various forms of lymphosarcoma.

Sections stained with phosphotungstic acid hematoxylin show the cell characteristics already described, except that the cytoplasm after this treatment is rather more granular than when stained in other ways, and most of the cells show near the nucleus a paler zone in which is situated two small intensely black staining granules interpreted as centrosomes. Whereas it is common to make out two of these dots, not infrequently only one can be distinguished, while in other cells, especially in the cells which contain more than one nucleus, three or four dots can be made out.

CASE X (Myeloma " Y ").[1] The case has been reported by Dick (*Trans. Chicago Path. Soc.*, vol. vi, 1903-1906, p. 168), from which the following brief clinical note and autopsy findings were abstracted. The patient was a man thirty-two years of age,who, in July, 1902, had suddenly lost his sight in both eyes. Three days later he regained his sight in the left eye. Soon his eyes began to bulge and he was operated on twice for retro-ocular sarcoma. On Aug. 12, 1903, he had an epileptic seizure, followed by headache which lasted twenty-four hours. At this time there was a growth about the left orbit continuous with the frontal bone, and both eyes showed choked disks. Removal of the tumor was attempted, but the patient did not survive the operation more than a few hours.

On Aug. 15 an autopsy was performed by Dr. Wells. He found on the ninth rib at the angle a swelling just palpable externally, which measured 7 x 4 cm. This nodule lay beneath the pleura except where a button-like mass projected through the pleura. The skull

[1] This tissue was sent me by Dr. H. G. Wells, of the University of Chicago, to whom I wish to express my sincere thanks.

showed a large operative defect in the frontal bone, 4 x 5 cm. At the outer angle of this there was a mass of tissue, 2 cm. in diameter, adherent to the bone, white and soft. More tumor tissue extended beneath the left zygomatic arch and was intimately connected with the bone. The bone was very soft and infiltrated with tumor. The entire left frontal lobe of the brain was occupied by tumor mass. No tumor metastases were found in the internal organs.

Stroma in this tumor is very slight in amount and is present only as fine connective tissue fibrils forming a reticulum in which lie tumor cells, at times closely packed together, at other times fairly well separated. (Fig. 10.) When closely packed, the cells are roughly polygonal in shape (Fig. 20); when loosely scattered, they are round or slightly oval. These cells average 12 x 9.7 microns in size. The cell outline is distinct, occasionally there is a suggestion of a cell membrane. The cytoplasm of many cells is finely vacuolated. Not infrequently these cells have a rather ragged, frayed-out border. In other sections many of the cells are very finely granular, almost homogeneous, and the vacuolated cells are less numerous. The cytoplasm in relation to the nucleus is quite abundant, and the nuclei almost always distinctly eccentrically placed in the cell. (Fig. 20.) The nuclei are round or slightly oval, with finely granular chromatin, often tending to group itself peripherally on the nuclear membrane. They measure 6.2 x 5.8 microns. Occasionally a cell shows a fairly distinct nucleolus. In many of the cells the nucleus shows shrinkage and has a more deeply uniformly staining nucleoplasm. A few cells show two or three nuclei. In some sections many of the nuclei show the chromatin collected in fairly coarse masses grouped peripherally on the nuclear membrane, and in

places these chromatin masses appear to have become free in the cytoplasm, though still more or less closely grouped together, so that we have a cell in which at one point are several small chromatin masses grouped together without any definite arrangement and apparently not within a nuclear membrane. In most of the tissue repeated search failed to reveal any mitoses but in one section a single nucleus in mitosis was found and this cell appeared to be a tumor cell.

In a number of the cells the cytoplasm has a distinct yellowish tinge, suggestive of hemoglobin staining, but it cannot be definitely stated to be hemoglobin owing to the unsatisfactory way in which the tissue takes the stain. However, this condition is rather more marked in those portions of the tumor in which hemorrhage has taken place. In the sections stained with phosphotungstic acid hematoxylin the cytoplasm shows a quite distinct tendency to take the hematoxylin stain and is finely granular. Centrosomes could not be made out in some of the sections, possibly owing to unsatisfactory staining with phosphotungstic acid hematoxylin, but were quite distinct in a number of cells in one section.

CASE XI (St. Paul, Myeloma).[8] A man of fifty-eight, a patient of Dr. T. W. Stumm, St. Paul, Minn., began in August, 1905, to have a feeling of weakness in the legs, which at first came on after a hard day's work, but soon increased in severity so that he could scarcely walk. His legs were now stiff as well as weak, and there was slight pain starting in the small of the back and radiating down the legs. After two or three months the

[8] This tissue was sent me by Dr. T. W. Stumm, of St. Paul, accompanied by a clinical history of the case, from which I have abstracted the above notes. I desire to express my sincere thanks to him for this courtesy. The case will be published in detail later by Dr. Stumm.

condition improved and he was able to do some work on the farm, but in the spring of 1906 the condition grew worse, and on Aug. 8 he entered the City and County Hospital in St. Paul. He could now walk around only a little by supporting himself by the bed or with a cane. He complains of pain in the small of his back, radiating down the thighs and legs, but when lying on his back rests very comfortably. Palpation with only very moderate pressure on the lower sides of the chests causes him to cry out with pain. This pain he locates in the dorsal region. When one taps along the vertebral column, he complains of pain in the lower dorsal region. He can only sit up by hanging his feet over the side of the bed and then holding on to the side of the bed with his hands. He holds himself pretty rigidly and moves slowly and cautiously in a spastic manner. Knee-jerks are much exaggerated and there is no ankle clonus. There were no very marked changes to be made out on physical examination other than these. He gradually became weaker, and for most of the time his temperature was one or two degrees above the normal. He died early in 1907.

Urine examined during his stay in the hospital showed no albumin and no special mention is made in the report of the presence or absence of albumose.

The tissue available for study from this case consists of several vertebræ preserved in formalin. Sections from these after decalcification show bone marrow and tumor quite intimately intermingled. (Fig. 11.) This fact renders it difficult in most places to positively separate tumor cells from cells which might be regarded as normal constituents of the bone marrow, and for this reason cell measurements were not made. However, there are foci here and there in which cells of quite uniform appearance are grouped together in the

same relation to each other as is common in the other examples of myeloma, and it seems fair to regard these cells as undoubtedly the tumor cells and not normal constituents of the bone marrow. Most of these cells are irregular in shape, polygonal from pressure of adjacent cells. The cell outline is fairly distinct with no indication whatsoever of a cell membrane. (Fig. 17.) The cytoplasm is finely granular and of a less homogeneous ground-glass appearance than was the case with preceding tumors. The cytoplasm is possibly slightly basophilic, though the staining reactions are not perfectly satisfactory in this regard.

The nucleus in relation to cell body is rather large and there is some tendency to an eccentric position of the nucleus. The nuclei themselves are vesicular. There is a distinct nuclear membrane and fairly fine chromatin granules with some slight tendency to peripheral grouping. In some cells a fairly distinct nucleolus can be made out, but this is not common. Scattered among these cells are cells with slightly smaller, more deeply staining nuclei, which may be considered as tumor cells in varying stages of degeneration. There are also some cells in which the chromatin granules are coarser and definitely grouped on the nuclear membrane.

There is nothing particularly notable in those parts of the bone marrow in which no tumor cells occur. The bone marrow is moderately cellular, indicating a fair degree of proliferative activity, and megakaryocytes are quite numerous. Mitotic figures occur in association with tumor cells, but it is not possible to say with certainty that these mitotic figures are not in intermingled cells normal to the bone marrow. In general, the cells in this tumor correspond in appearance to the cells in the previously de-

scribed tumors, but owing to their diffuse distribution in bone marrow in which a large variety of cells is normal, it does not seem fair to state that any transition between tumor cells and fairly typical plasma cells can be made out. The transition is suggested, but in a tumor of this structure error of interpretation can be easily made. However, it seems justifiable to include this tumor in the group and to consider it as a true myeloma, but it would not be possible to base very definite conclusions as to cell structure on a study of this case alone. That myelomata may sometimes grow diffusely in the bone marrow, as in this case, was well shown in Case I, in which the cells are relatively larger and more easily distinguishable from any cell of the normal bone marrow. In that case small groups of tumor cells could be easily recognized in the bone marrow of the femur, which macroscopically appeared perfectly normal, and entirely different in appearance from the other bones examined in which the marrow had practically been entirely replaced by tumor cells. In connection with the other tumors I think the cytology of this case can be understood and is properly to be interpreted as I have done above.

In my previous paper were collected from the literature those cases in which cell structure was described in detail sufficient to show the character of the cells composing the tumors. Those cases, in so far as may be judged from their descriptions, show a quite uniform cell type, though there are considerable minor variations in cells in the different tumors. For eight of the cases collected from the literature it is claimed by their reporters that the cells find a close analogy in the plasma cell.

Of six it is believed that the cells bear a close relation to immature myelocytes. In one, the case of Sternberg, cytoplasmic granulation is described. In Ribbert's case an erythroblastic nature is claimed. In some cases no attempt to homologize the cells was made.

Since then several other cases have been reported. Permin (*Virch. Arch. für path. Anat.*, 1907, clxxxix, 439) describes three cases in which the cells measured 9, 8.5 and 8.5 microns respectively. It is evident from his descriptions and drawings that these tumors are essentially identical in structure. The cells he would group as premyelocytes. Hueter (*Münch. med. Wochenschr.*, 1907, liv, 811) reported one case briefly at a medical meeting. He described the tumor cells as round or polymorphous without granulations in the cytoplasm. He terms the tumor cells pseudomyelocytes. Charles and Sanguinetti (*Brit. Med. Jour.*, 1907, i, 196) give the following description of the cells in a typical case: The cells are of three types: round cells uniform in size with a large pale nucleus and large protoplasmic contents which is granular in character; round or polyhedral cells with a small, deeply staining nucleus and finely granular protoplasmic contents; large round cells with large, round, deeply staining nuclei and finely granular protoplasmic contents. They regard the tumor cells as resembling cells in the normal marrow which are the predecessors of myelocytes. Dévé (*Normandie med.*, Rouen, 1907, xxii, 289 and *Rev. méd. de Normandie*, Rouen,

1907, viii, 207) has reported a case according to the title of his paper, but his paper was not available for verification. The question naturally arises, How far in the light of these cases can the histogenetic source of the tumor cells be determined?

A study of the bone marrow from a variety of cases shows that but two types of cell have any very close resemblance to the cells of these myelomata. Both are cells which have a slightly basophilic cytoplasm, distinct cell outline but no cell membrane. Both have a nucleus, frequently eccentric in position, with a distinct nuclear membrane and fairly constant nucleolus. In the one the nucleus is palely staining, with fine chromatin masses generally scattered throughout the nucleus, sometimes clumped more or less toward the center, but without any tendency to a mural arrangement. These cells (Fig. 26) belong to the myelocyte series, an early stage of development, usually before the specific granulation in the Ehrlich sense takes place, and are numerous in all active marrows. They may be called premyelocytes.

In the other cell (Figs. 24 and 25) the nucleus stains more deeply, the chromatin masses are coarser, there is rarely any central clumping of the chromatin masses. A nucleolus is a more constant feature. These cells appear to be constantly found in bone marrow. They are usually infrequent and never in large numbers. The maximum that I have ever found are scattered groups (Fig. 25, two cells in focus) of five

or six cells with a few single cells, so that about every other field of a Zeiss 2 mm. objective and 4 ocular would show at least one of these cells. I have never been able to find any evidence of developmental changes in these cells. Their nature is not certain. They seem to have no relation to the formation of erythrocytes or polynuclear leucocytes. Of their relation to the lymphocyte series I can give no positive evidence. They appear closely related. Their closest analogue outside of the bone marrow is the plasma cell from which they differ in being slightly larger both cell body and nucleus, in having a less homogeneous ground-glass cytoplasm, in being rather less basophilic, in having not quite so coarse chromatin granules; but all these differences are of minor degree and do not serve to distinguish sharply these cells from the plasma cells of inflammatory tissue. However, as there are slight differences, I prefer to speak of these cells in the bone marrow as bone marrow plasma cells, and regard them as in some way related to the lymphocyte series of cells.

Which of these cells stands closest to the myeloma cell? As is evident from the description of the cells in the myelomata reported by me and by others, there is considerable minor variation in the cell picture. The features most constant in the tumor cells are cytoplasm finely granular or slightly vacuolated, slightly basophilic; a nucleus eccentric in position, with a tendency to a mural arrangement of chromatin and a nucleolus; the

presence of centrosomes. There is some variation in cell size, the average of measurements in [9] each case being: [See table on opposite page.]

To compare with these I have made measurements of a number of cells in the bone marrow. The average of these is:

For myelocytes and premyelocytes from different cases:

11.5 x 9.25 microns;	nucleus,	8.0 x 7.5 microns.	
11.8 x 8.25 ,,	,,	7.2 x 6.5	,,
12.25 x 9.7 ,,	,,	8.5 x 7.2	,,

For bone marrow plasma cells from different cases:

9.7 x 7.0 microns;	nucleus,	5.1 x 4.6 microns.	
8.6 x 6.6 ,,	,,	5.3 x 5.0	,,
9.9 x 7.5 ,,	,,	5.6 x 4.8	,,

From these measurements it is evident that the cell body and nucleus of the myelocytes are rather larger than those of the tumor cells. The bone marrow plasma cells agree in size with the cells of those tumors which have the smaller sized cells. cases seem to me to present more similarity to the A glance at the cell descriptions in these will show that these tumors have cells which agree closely in structure with the bone marrow plasma cells. The other tumors have cells which, while retaining the characteristics in part of the plasma cells, yet show differences. Still these differences, though in the direction of the premyelocyte, do not often give a cell so large as the premyelocyte, and when compared side by side the cells appear to be more

[9] All these measurements were made on cells in tissue hardened in Zenker's fluid, embedded in paraffin and stained with eosin and methylene blue, except cases VII, VIII. The same lenses and micrometer were used throughout.

Case VI,	cell body,	8.4 x	4.2	microns;	nucleus,	4.2 x	4.1	microns.
Case IV, sternal part,	,,	8.5 x	5.5	,,	,,	5.7 x	5.4	,,
Case VII,	,,	9.0 x	7.7	,,	,,	5.3 x	4.6	,,
Case IV, orbital part,	,,	9.4 x	7.6	,,	,,			
Case V,	,,	9.9 x	6.4	,,	,,	6.9 x	5.0	,,
Case IX,	,,	10.2 x	8.7	,,	,,	6.9 x	6.1	,,
Case II,	,,	10.4 x	6.8	,,	,,	6.0 x	6.0	,,
Case III,	,,	10.5 x	6.8	,,	,,	7.2 x	6.4	,,
Case VIII,	,,	11.2 x	10.0	,,	,,	6.6 x	6.1	,,
Case I,	,,	11.4 x	7.7	,,	,,	8.1 x	7.2	,,
Case X,	,,	12.0 x	9.7	,,	,,	6.2 x	5.8	,,

closely homologous with the bone marrow plasma cells than with the premyelocytes. This is certainly true also for the cells in many of the tumors reported by others.

In other words it seems possible to arrange the cells of these tumors in series so that between the cells of succeeding cases the differences are slight, though the differences between the cells at the extremes are fairly great. This is well shown by comparing in series the photographs, Figs. 12 to 23. The cells of one tumor described by me are almost identical in structure with plasma cells of the marrow, and those in four others are but very slightly different. The cells in the other cases seem to me to present more similarity to the plasma cell than to the myelocyte. If the myelocyte is assumed to be the ancestral cell the departure from the type is very much greater. (Compare the premyelocyte in Fig. 26 with cells in the series given above.) It is probably not possible to give any convincing proof of the ancestry of these cells. The cases studied side by side and in comparison with bone marrow cells leave the impression that we have in these tumors a development from certain bone marrow cells, which I have considered to be bone marrow plasma cells. Whether this is true for all reported cases is exceedingly difficult to say, especially for those cases in which the cells are not described in much detail. Possibly some cases, as that of Sternberg, in which neutrophilic granules are described, may have to be regarded as an exception.

In addition to this histological evidence as to the nature of the cells in myelomata the following observations may be considered in favor of their plasma cell nature though it is not claimed that they are conclusive. Eduard Müller (*Deut. Arch. für klin. Med.*, 1907, xci, 291) has described a simple method of testing the proteolytic leucocytic ferment by means of blood serum plates at a temperature of 55° to 60° Centigrade, thus inhibiting the growth of bacteria. Under these conditions leucocytes digest the blood serum, producing a depression where they come in contact with the serum. This ferment action, it has been already pointed out is not destroyed by the preservation of the cells in formaldehyde. At my suggestion Dr. Channing Frothingham, Jr., has tested in this way portions of tissue from cases I and VIII which had been preserved in alcohol. As a control bone marrow from a case of myelogenous leukemia similarly preserved in alcohol for a longer time was tested. With the tumor tissue no digestion of the blood serum took place while with the myelogenous leukemia bone marrow definite digestion resulted. Were the tumor cells histogenetically related to myelocytes, it might be supposed that they would cause digestion of the serum. This evidence for a myelocyte origin of the tumor cells is, to say the least, lacking.

Ribbert's (*Centralbl. für allg. Path.*, 1904, xv, 337) contention that the case studied by him was composed of erythroblastic cells is not supported by these cases. The frequent presence in my

cases of cells stained with hemoglobin and resembling nucleated red blood corpuscles, as already described, suggests the possibility that a similar condition may have been present in Ribbert's case. In my cases it seems very certain that these cells result from a combination of cell degeneration and hemoglobin staining. Such hemoglobin staining of plasma cells is by no means uncommon, especially in the spleen where I have observed it many times, and this fact may be taken as some slight further evidence of the plasma cell nature of the tumor cells.

Certain nuclear changes regarded as degenerative phenomena are of frequent occurrence in these myelomata. Almost all show nuclei in varying stages of shrinkage. As the nuclei shrink, they stain more diffusely and more deeply until finally all evidence of intranuclear structure is lost. More interesting are the nuclear pictures shown in cases II, VIII, IX and X, in which there are many nuclei in which a process of nuclear segmentation has taken place, which results in the formation of a varying number of spherical chromatin masses of varying size and homogeneous structure. With both of these changes, as already pointed out, hemoglobin frequently is present in the cytoplasm.

In descriptions of myelomata the absence of mitotic figures has been quite often noted, and it has been suggested that the cells divide only by direct division. However, in my cases typical mitoses were found in cases II, III, IV, V, VIII,

IX, X and XI(?), [10] and were quite numerous in some of these. Their absence in other cases is to be explained, I think, by the slow development of many of these tumors rather than by any peculiarity of the tumor cells. This theory is further supported by Case IV, in the sternal portion of which mitoses were easily found, while they were excessively rare or absent in sections from the orbital portion.

There is nothing in these tumors to suggest any transformation of cells along the line of development from premyelocyte to polymorphonuclear leucocyte. Sternberg is the only observer who has succeeded in demonstrating neutrophile granules in the cells of a myeloma. This fact in this single case does not seem sufficient evidence on which to base the opinion that all myeloma cells are myelocytes in some stage of development when we consider the great similarity of the cells in very many cases to plasma cells. If more cases like Sternberg's are accumulated, it would justify a subdivision of myelomata into (*a*) those with cells resembling plasma cells, and (*b*) those with cells resembling myelocytes. Even then it would still be possible without claiming a histogenetic relation between plasma cell and myelocyte to form a tumor group, having the main characteristics already described for the myelomata, in which all cases could be arranged in series with a tumor composed of cells identical

[10] In Case X only one mitotic figure could be found. In Case XI there is the possibility that the cells found in mitosis were not tumor cells but marrow cells.

with plasma cells at one end of the series, and a tumor with cells identical with myelocytes at the other, while between would come cases whose cells represented a gradual transition from one to the other. Such a group would contain tumors showing no greater differences than occur within all other tumor groups, such as sarcomata, carcinomata, etc. However, with regard to the tumors actually studied by me, all would be grouped at the plasma cell end of such a series.

A study of these cases and a review of those reported in the literature strongly suggests that the myelomata are true tumors rather than the bone marrow manifestations of a systemic disease as claimed by Pappenheim (*Folia hematologica*, 1907, iv, Supplement Heft 2, 215) and that they belong to that general group of tumors which tend to extend or metastasize chiefly in a single system of the body. A common example of this tumor group are the lymphosarcomata or lymphocytomata. However, metastasis into the viscera does take place in some of the cases of myeloma, and many show a distinct invasive type of growth where they break through their bony bounds and infiltrate adjacent tissue. This in itself seems sufficient evidence for regarding the myelomata as tumors in the commonly used sense of that word.

SUMMARY.

A histological study of eleven cases of myeloma shows a striking similarity of cell structure with differences of minor degree. The common char-

acteristics of the cells are a finely granular, slightly basophilic cytoplasm, an eccentrically placed nucleus, a nucleolus, centrosomes, a nuclear membrane and a tendency to mural arrangement of the chromatin. Certain nuclear changes, regarded as the results of degeneration are commonly found. Mitotic figures occur in most of the cases studied by me, though absent in a few.

Myelomata are to be classed with the tumors. They tend to remain localized in the bone marrow but almost all show evidence of invasive growth into adjacent structures, and in a few metastasis has taken place. These tumors then are malignant in the usual sense of the word, but their malignant properties are apt to appear relatively late in many cases.

With these characteristics there is a greater resemblance of the tumor cells to bone marrow plasma cells than to myelocytes. In most of the cases reported by other observers the cells show these characteristics and these tumors from a group within which the cells of individual cases show no greater variation than occurs in other tumor groups.

DESCRIPTION OF PLATES.*

Figs. 1 to 11. Low power (425 diameters) fields from eleven cases to show cellular character and scant stroma of myelomata.

Figs. 12 to 23. Cells (1,500 diameters) from each tumor, arranged in series to show the slight variations in cell structure.

Fig.	12	from case	III
"	13	" "	I
"	14	" "	VIII
"	15	" "	VIII
"	16	" "	V
"	17	" "	XI

* These photographs were made by Mr. L. S. Brown, at the Massachusetts General Hospital, for whose careful work I wish to express my thanks.

Fig. 18 from case II
" 19 " " VII
" 20 " " X
" 21 " " IX
" 22 " " IV
" 23 " " VI

Fig. 24. Bone marrow plasma cell (1,500 diameters) from a case of pernicious anemia.

Fig. 25. Group of bone marrow plasma cells (1,500 diameters) from a case of cirrhosis of the liver.

Fig. 26. Premyelocyte, plasma cell and eosinophilic myelocyte (1,500 diameters) from a case of cirrhosis of the liver.

Fig. 27. Cells showing nuclear changes (1,500 diameters). From Case VIII.

THE USE OF HUMAN MILK IN TYPHOID FEVER TO INCREASE THE BACTERIOLYTIC POWER OF THE BLOOD.

BY FRANCIS P. DENNY, M.D., BROOKLINE, MASS.,

Medical House Pupil, Massachusetts General Hospital, 1895; Visiting Physician to the Massachusetts Infant Asylum; Physician to the Boston Dispensary.

THE problem to be solved in devising an effective serum treatment of typhoid fever may be fairly well represented by the following experiment.[1] If to a drop of a bouillon culture of typhoid bacilli there is added a drop of the serum of a typhoid patient and then a drop of serum of a normal healthy individual, the bacilli are quickly destroyed. If the typhoid serum or the normal serum alone is added no considerable number of the bacilli will be destroyed.

Bacteriolysis, or the destruction or digestion of the bacilli in the above experiment, is brought about by the combined action of two substances: (1) the *immune bodies* (amboceptors) in the typhoid serum, which have been given off by the cells of the body during the disease, and (2) the *complement* (alexins), a ferment present in normal blood which when bound to the bacterial cell by the immune body has the power of digesting the bacteria. In the normal serum there are insufficient immune bodies to destroy the bacilli;

[1] Richardson: Jour. Med. Res., vol. vi, 1901, 187.

in the typhoid serum there is absent the necessary complement to bring about bacteriolysis.

With these facts in mind one would seem justified in concluding that (1) to prevent typhoid fever in a healthy individual one should increase the immune bodies in the blood to combine with the complement already present in destroying the invading bacteria; and (2) to destroy the bacilli when the disease has developed one should increase the complement to act with the immune bodies already present.

There is abundant proof that the first conclusion is correct. The inoculation of an immune serum in a healthy individual will give a temporary (passive) immunity, while a more permanent (active) immunity can be secured by increasing the immune bodies by means of inoculations of dead bacilli, as shown by Wright in the English army.

There is, at present, no proof that typhoid fever can be effectively treated by increasing the complement, because as yet no method has been devised of increasing it. The normal serum of animals cannot be used as a source of the complement, because the inoculation of such a serum results in the production of an anticomplement which inhibits bacteriolysis. There is need, then, for a human source for the complement.

The use of human milk to increase the complement in typhoid fever was suggested to the writer by the work of Moro [2] on the bactericidal

[2] Moro: Wien. klin. Wochenschr., vol. xiv, 1901, p. 1073.

power of infants' blood. Using the plate method, he found that the average of a large number of tests made under exactly similar conditions showed that:

	Per cent of bacteria.
Maternal blood (placental) killed	58.9
Blood of older children killed	46.3
Blood of artificially fed infants killed	33.4
Blood of breast-fed infants killed	77.0

The bactericidal power of the infant's blood at birth corresponds very closely with the placental blood. Following the breast feeding there is an increase, so that it is considerably greater than that of the mother's blood, while on an artificial diet there is a rapid falling off.

Pfaundler [3] and Moro were able to demonstrate the complement in the milk of several species of animals. They found it difficult to demonstrate the complement in human milk because, as they claim, there are substances in the human milk which inhibit its action. They believe, however, that it is present.

The complement is almost invariably diminished in atrophic infants, and Pfaundler [3] believes that infantile atrophy is caused by a deficiency of the complement — at least of a *tropholytic* complement — through whose action the nutrient material is anchored to the cell and discharged from it. He believes that the deficiency of the complement is made good in the breast-fed infant by complement brought from the mother through the milk. There is abundant proof that protective

[3] Pfaundler: Münch. med. Wochenschr., Dec., 1907.

substances pass from the mother to the child in the milk. Thus it has been shown that diphtheria antitoxin in the mother's blood is excreted in the milk and is so taken into the infant's circulation. Antitoxin cannot pass, however, through the milk to an animal of a different species.

In whatever way human milk may act, whether by increasing the complement or by some other as yet unknown immunizing property, it certainly gives the nursing baby a remarkable immunity against infections. For example, artificially fed infants living in institutions or asylums have a very high mortality from infectious processes of different kinds, while infants partially fed on human milk can live side by side with the artificially fed infants in such an institution, under exactly similar conditions, except for the human milk, and appear to thrive as well as in a good private home.

It is not merely an immunizing power against infections that is given the infant by human milk. As the literature abundantly shows,[4] human milk is also *curative* in its action, even in comparatively small amounts. This curative effect is seen not merely in infections of the gastro-intestinal tract, but in other infections; for example, in furunculosis and other suppurative conditions.

This protective power of human milk is not limited to the first year of life. The mothers in the tenement houses know that if they can nurse

[4] Denny: Jour. Am. Med. Asso., 1906, vol. xlvii, p. 1904.

their babies two or three times a day during the second summer, the babies are much less likely to get sick. Often these mothers will leave their babies all day while they go to work (the baby in the meantime being fed on the regular family diet), but several times through the evening and night the baby will nurse. There is little milk in the mother's shrunken breast, and that little is undoubtedly of poor quality as a food, but it brings from the mother certain elements which protect the child from infections.

The curative effect of human milk is also seen during the second year. I have recently had under my care at the Massachusetts Infants' Asylum three children between one and two years of age to whom human milk was given. All were sick with severe gastro-intestinal infections, and two of them were almost moribund when first given the human milk. The beneficial effects were as prompt and decided as in any case under a year, that I have ever seen.

The question therefore arises, At what age does human milk cease to aid the individual in resisting infections? If it is of value through the second year, why not through the third and fourth and even into adult life? Are we not as well justified in concluding that a treatment which is effective for a child will be effective for an adult, as we are in reasoning from the results of animal experiments, as to the results of a given treatment in man?

It has not been proved that the protective

power of human milk depends on the complement which is brought from the mother; in fact, Wasserman [5] explains in a different way the greater bactericidal powers of the blood of breast-fed infants: the soluble albumin of human milk can pass with little change into the blood of the infant, while the albumin of cow's milk, being the albumin of a different species of animal, cannot so pass, but must be transformed into human albumin by the action of ferments in the intestinal wall. Wasserman believes that the ferments which transform the foreign albumin are identical with the complement. In accordance with his theory, therefore, the bactericidal power of the artificially fed infant is low because the complement is largely employed or used up in transforming the albumin of the cow into the human albumin of the infant.

The use of human milk, an homologous albumin, as a food in typhoid fever means that less complement would be used for transforming the food, and therefore more would be free to combine with the immune bodies for the purpose of bacteriolysis.

This also suggests a reason for restricting the foreign albumin in the diet of a typhoid patient; and a diet with carbohydrates would seem more rational than the exclusive milk diet so commonly employed.

The theories of Escherich [6] suggest that human

[5] Wasserman: Deut. med. Wochenschr., 1903, vol. xxix, p. 16.
[6] Escherich: Wien klin. Wochenschr., 1900, vol. xiii, p. 1083.

milk might be of value in typhoid fever in other ways than by increasing the complement. Escherich believes that those ferments of the internal secretions which regulate and control the growth of the tissues (Stoffwechsel-fermente) and which are the products of the so-called ductless glands, pass from the mother to the child in the milk. The nursing period is thus a continuation of the intra-uterine dependence, the child receiving substances through the milk similar to those received through the placental circulation.

These ferments of the internal secretions, if present, might well be of value to the typhoid fever patient. We know that glandular tissues suffer severely from the effects of the typhoid toxins. Thus the secretions of the digestive glands are much impaired and it seems probable that the so-called ductless glands suffer a similar impairment of their function.

There is a tendency for the tissues and organs of the body when severely injured to revert in many of their characteristics to an earlier or embryological condition. Thus in severe anemias, the blood takes on certain fetal characteristics. May it not be that metabolism in the typhoid patient, whose tissues are severely damaged by the prolonged toxemia, resembles in some respects that of the infant, and may not the ferments of the internal secretions, if present in the human milk, be of value to the typhoid patient in his struggle with the disease? From this point of view, human milk is a form of *organo-therapy*.

The foregoing considerations may be briefly summarized as follows:

1. Theoretically an increase in the complement is indicated in the treatment of typhoid fever, but no method of doing this has yet been devised.

2. The blood of the breast-fed infant has greater bacteriolytic power than that of the artificially fed infant.

3. There is some reason for believing, although it is not proved, that the complement passes from the mother to the young of the same species through the milk.

4. Human milk gives the infant a marked immunity against infections, and is curative in its effects when used in the treatment of infections.

5. The immunizing and curative effect of human milk appears to be marked in the second as well as in the first year of life, and there is no reason to suppose that these effects are limited to these first two years.

6. According to Wasserman, a foreign albumin in the food is transformed into the albumin of the body by the action of the complement; the complement, therefore, is low in the artificially fed infant because it is used up in this work. The giving of an homologous milk to a typhoid patient should therefore set free some complement which would thus be available for the purpose of bacteriolysis.

7. According to the theories of Escherich, various ferments of the internal secretions pass from the mother's blood to the infant through

the milk. The so-called ductless glands may suffer an impairment of their functions in typhoid just as do the digestive glands, and these ferments if present in the milk would be of assistance to the patient.

The foregoing considerations made it seem desirable to see if any beneficial effects followed the giving of human milk to typhoid fever patients. Certainly no ill effects could follow the use by an adult of a food which is known to be the most easily digested and assimilated by the human being at the age when its power of digestion and assimilation is at its lowest stage of development.

During November and December, 1907, seven patients at the Boston City Hospital were given human milk which had been collected under the supervision of the writer. Five of these cases were on the service of Dr. G. B. Shattuck, and two on that of Dr. J. L. Ames, to both of whom I am indebted for the privilege of reporting the cases. I am also greatly indebted to Dr. E. P. Joslin for much valuable assistance in the work.

The milk was collected by Mrs. A. M. Henderson, a trained nurse. After visiting a large number of nursing mothers living in the tenement house districts, a few were found who had a superabundance of milk. These mothers and their babies were all examined by me and found to be healthy before the milk was used. Precautions were taken to have the milk drawn in a cleanly

manner, and put in sterile bottles and then kept at a low temperature. The ability of the mothers to draw off the milk increased markedly after the experience of a week or two. One mother was able to give us over a quart a day.

The idea of taking the milk intended for a helpless infant for the use of an adult is not wholly a pleasant one. In our experience, however, there seemed to be no objectionable features. As the milk was taken only from mothers who had more milk than their own babies required, all of the babies continued to thrive while the mothers were contributing the milk. Moreover, the general comfort and prosperity of the family was materially increased by the money which was paid for the milk.

Except for the human milk, which replaced a corresponding amount of cow's milk in the diet, the treatment of the typhoid patients was according to the hospital routine, with cold baths when the temperature was above 102.5°.

The human milk was given to the patients in the same way as the cow's milk, and was readily taken. Those patients who were somewhat dull did not appear to notice any difference. The taste is not unpleasant; it is sweeter and less heavy than the cow's milk, and has a slightly acrid taste, suggesting cow's milk well diluted with a carbonated water. Two patients taking the milk were nauseated on the same day, which suggested that the cause of the disturbance was something peculiar to the milk of that day rather

than to the human milk as such. As far as is known only one other patient was nauseated while taking the milk. When one considers how common a symptom nausea and vomiting is in typhoid fever, one can say that the milk was well borne. One patient thought his bowels moved better while taking the milk.

It was hoped to give the milk to a much larger number of patients, but after the collections were begun, the cases available for a trial proved to be much fewer than was anticipated. Four of the seven cases were not satisfactory tests; in Cases III and V, the temperature had already begun to fall when the milk was started; Case VI proved to have a septic endocarditis in which there was no possibility of benefit, and Case VII did not have typhoid at all.

CASE I. L. G. Female. Thirty-four years. Single. Entered hospital Nov. 12. For two weeks had felt tired, four days fever, diarrhea, headache.

Examination: Moderate prostration, tongue coated, a few râles in chest, spleen palpable, rose spots, Widal positive on Nov. 16.

Nov. 14 to 28, bacteriolytic* milk given, 20 to 30 oz. daily, average, 28.6 oz., total 13 qts. On Nov. 14 and 15 the temperature reached 104°, but on the following days it was lower, being normal Nov. 29. On the 30th, two days after the milk was stopped, there was a short rise of temperature to 104°, which was the beginning of a ten days' relapse. Dec. 23, discharged well.

* Human milk here and throughout the records is called "bacteriolytic milk."

CASE II. R. E. Female. Twenty-two years. Single. Entered hospital Nov. 15. For one week headache, fever, chilliness.

Examination: Marked apathy and prostration; tongue dry and fissured; heart irregular, systolic murmur at apex, abdomen soft, spleen felt, no rose spots.

Nov. 16, Widal and blood culture positive.

Nov. 19 to 26, given bacteriolytic milk 24 to 35 oz. daily, average 30 oz., total 7½ qts.

Nov. 26, vomited after taking the milk, which was then omitted.

Dec. 3, patient had a profuse hemorrhage from the bowels. General condition poor. Vomiting for past two days.

Dec. 5, several more hemorrhages during past few days, leaving patient very weak. Died 8 P.M.

CASE III. F. Q. Male. Seventeen years. Single. Entered hospital Nov. 21. For four days weakness, chilly sensations, headache, diarrhea.

Examination: Moderate apathy; tongue has thick white coat, spleen felt; rose spots.

Nov. 22, Widal positive (?).

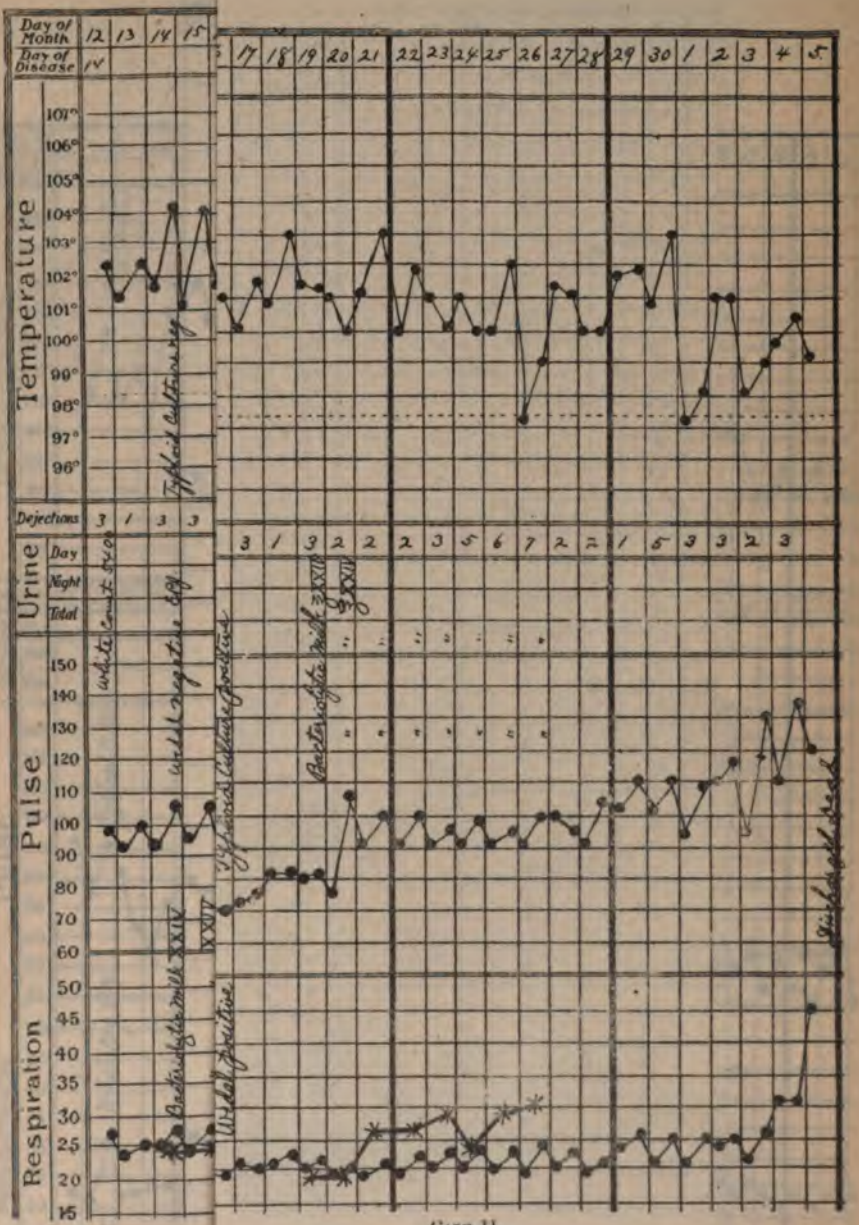
Nov. 29 to Dec. 2 bacteriolytic milk 33 to 76 oz. daily, average 59.7 oz., total 7½ qts. Temperature was already dropping when milk was started, and reached normal two days later. Was a mild case.

CASE IV. C. L. Male. Twenty-nine years. Married. Entered hospital Nov. 30, 1907. Eight days unable to work and had felt ill for a week before that. Headache, nausea, epistaxis, constipation.

Examination: Moderate prostration and apathy, tongue coated, abdomen soft, spleen felt, rose spots.

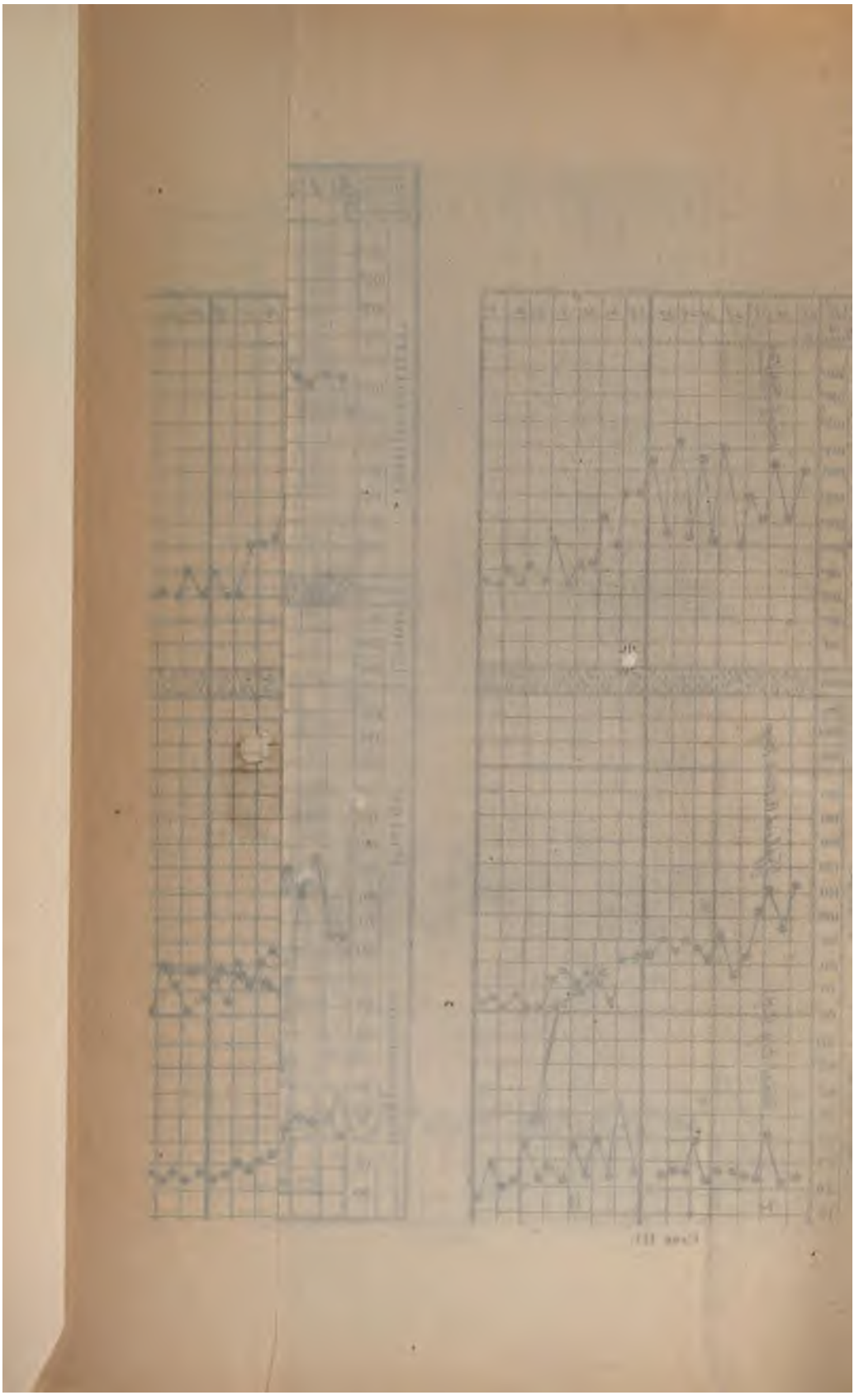
Dec. 3, Widal and blood culture positive.

Dec. 2 to 12, bacteriolytic milk, 33 to 82 oz. given daily, average 62.9 oz., total 21 qts. 20 oz.



Case 11.

patients received.



On Dec. 6, after taking the milk four days, the temperature dropped to normal, but went up in the evening to 102° and remained 100° to 102° for the following week. While the milk was being taken the patient thought his bowels acted better than before or after. Convalescence was uneventful. Discharged well.

CASE V. W. C. Male. Twenty-six years. Single. Entered hospital Dec 5. Is said to have had typhoid eight months before. For one week feeling poorly. Headache and backache, chilly, fever, constipation.

Examination: General condition good. Moderate apathy and prostration, abdomen soft, spleen not felt, no rose spots. Widal positive.

Dec. 13 to 25. Bacteriolytic milk 64 to 79 oz. daily, average 74 oz., total, 18½ qts. The course of the fever in this case lasted only three weeks, but the symptoms were severe.

CASE VI. C. E. Female. Twenty-six years. Single. This patient had typhoid fever with septic endocarditis and multiple abscesses. Bacteriolytic milk given during the tenth week, 8 to 24 oz. daily, average 18.3 oz., total 4 qts. The milk was well borne, but as was to be expected with this complication, no improvement followed and she died in the fourteenth week.

CASE VII. S. H. Female. Entered hospital Dec 20. Ill three days. Temperature 102.2°. Probable diagnosis at entrance was typhoid fever.

Dec. 21 to 25 given bacteriolytic milk, 66 to 88 oz. daily, average 73 oz., total 11½ qts. Temperature normal on Dec. 24. Widal was never positive.

The course of the disease in Cases I to V can best be followed by referring to the accompanying charts. The amount of human milk in ounces is indicated by the starred lines.

In Case II, a severe typhoid, there was no improvement while taking the milk. In Case I, the temperature began to be lower after two days on the milk. In Case IV the temperature began to fall on the day following the giving of the milk, and after four days there was a rather unusual temporary drop to normal. In Cases III and IV, where the temperature had already started to fall when the milk was first given, the temperature curve shows a more abrupt fall than is common in typhoid fever.

It is impossible to determine whether the human milk modified in any way the course of the disease in these patients. There were certainly no striking effects produced, and the course of the fever in all of the cases was such as might be seen in patients on the regular diet. It is very desirable that the milk should be tried in a larger number of cases and that a study should be made of the blood of the patients taking the milk.

An important factor in the etiology of typhoid fever that as yet we do not understand is the question why the young adult in the prime of bodily health and vigor is more susceptible and less resistant to the typhoid infection than are infants and young children. It may be that human milk will be found of more value to adults and children in infections to which infants are peculiarly liable.

This work has shown that drawn human milk can be easily obtained in considerable amounts, and that it is readily taken and well borne by the

adult. This work has not proved that human milk is of value in typhoid fever, but it is hoped that it will serve to suggest, as a field that well merits further investigation, the question:

Can the protective power against infections which human milk gives to the infant be of value to human beings after the first two years of life?

BRONCHOPNEUMONIA: ITS CLINICAL TYPES IN RELATION TO ETIOLOGY.

BY CHARLES HUNTER DUNN, M.D., BOSTON,

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MODERN tendencies in therapeutics are coming to demand more and more an etiologic rather than an anatomic basis for the classification of disease. It is the increasing knowledge of the causes of disease which has given the stimulus to the study of the problem of immunity, a study which has produced and is producing our most brilliant therapeutic achievements; and our chief hope for the future looks to increased knowledge of causes and their mode of action as its basis. Whether our treatment be prophylactic or curative it is not anatomic lesions which we are to combat, but their causes. When the same anatomic lesions are produced by a variety of causes, the essential differences for purposes of scientific study looking toward cure are greater than when a variety of lesions is produced by the same cause. Hence a classification based on causes is to be preferred whenever possible.

Unfortunately, the clinical manifestations of disease usually owe their specific character and distinguishing peculiarities rather to the anatomic lesions than to the specific etiologic agent,

characteristic symptoms being due to impairment of function from local anatomic conditions, rather than to any peculiar effect of the infecting organisms. Where specific organisms give rise to peculiar and characteristic lesions, no difficulty is encountered in classification, but it is in cases where the lesions produced are not characteristic that difficulties arise.

Bronchopneumonia is an example of this latter class of diseases. The term means an affection of the lung showing certain definite anatomic lesions, and it is upon the definite character of these lesions that bronchopneumonia rests its title to consideration as a disease entity, a title which would have no basis at all if our classification of diseases were wholly put upon an etiologic basis. We know that the lesions of bronchopneumonia are produced by a variety of pathogenic organisms, although comparatively little attempt is usually made to differentiate etiologic types. The pathologist at autopsy is usually content, upon recognizing the lesion, to call the case simply bronchopneumonia, without any further inquiry into the probable cause of the lesions, and from this fact I infer that the various pathogenic organisms have been found to produce no specific peculiarities in the lesions. I attempted to verify this inference by a study of autopsy records, but was unable to do so because I found that while the description of the lesions was most thorough, a bacteriologic study had not been made with commensurate completeness.

Nevertheless, bronchopneumonia presents itself to the clinician as a disease with distinctly varying manifestations, which fact suggested the possibility of dividing it into distinct clinical types. There seems also to be a certain relation between the clinical type and the prognosis. It has been recognized that there is also a certain amount of connection between the etiology and the prognosis, for example, that tubercular bronchopneumonia is usually fatal, while influenza bronchopneumonia is apt to recover. At once the question arises, Is there any relation between the clinical type and the etiology? for if so, such relationship would be of immense practical value to the physician when confronted by the question of prognosis.

The study of the sputum in pneumonia has thrown great light upon the question of etiology. It has been shown that the sputum is fairly characteristic in pneumonia produced by the pneumococcus only, and by the bacillus of influenza. The presence of tubercle bacilli in the sputum is considered proof of tubercular pneumonia, and even the pneumonia produced by the pyogenic cocci or by mixed infections can frequently be recognized as such.

Unfortunately, bronchopneumonia is chiefly a disease of early life, in which a satisfactory specimen of sputum is usually extremely difficult to obtain. A correspondence between clinical and etiologic types would therefore be of great added utility, if there is any such correspondence.

In the year 1903, there was a small outbreak of whooping cough in the Children's Hospital, a number of cases of which were complicated by bronchopneumonia. In children with whooping cough, it is almost always easy to obtain specimens of sputum, and I examined a number of such specimens. The bronchopneumonia presented itself in various clinical forms, and the few cases which I observed at that time seemed to suggest that there was some correspondence between the clinical type and the bacteriologic findings in the sputum. Since then I have been carrying on, rather intermittently, further investigations of this subject, in cases which did not have whooping cough, with efforts to obtain specimens of sputum by special methods, and by thorough study of cover-glass preparations taken from various parts of the lungs at autopsy, when the opportunity presented itself. The cases are still comparatively few, on account of the difficulty of obtaining satisfactory specimens. My aim is to present these results in comparison with the clinical type of the disease.

My records include 53 cases. In 31 of these cases the diagnosis of the probable etiology was based on examination of the sputum obtained during life, while in 22 cases it was based on the results of post-mortem examinations.

The results of the examination of the sputum and of the lungs post-mortem permit a division of the cases into 4 classes.

1. Five cases in which cover-glass preparations

showed pneumococci only, or in very large proportion, both within and without the leucocytes. The appearance in these cases was exactly the same as that seen in cover-glass preparations of the sputum of lobar pneumonia. While other organisms were present in small numbers, the appearance suggested that the lesions in these cases were chiefly due to the pneumococcus only. This group will be spoken of as the pneumococcus group.

2. Seven cases in which the influenza bacillus was found in such enormous predominence, both within and without the cells, that the appearance suggested that this bacillus was the chief or only cause of the lesions. This group will be spoken of as the influenza group.

3. Twelve cases in which either the tubercle bacillus was found in the sputum (4 cases), or in which the characteristic lesions of tubercular bronchopneumonia were found at autopsy (8 cases). This group will be spoken of as the tubercular group.

4. Twenty-nine cases in which cover-glass preparations suggested a mixed infection, a variety of micro-organisms being found, no one in such predominance as to suggest that it could be considered the chief cause. Pneumococci were usually present to a varying extent in these cases. Associated with them were found staphylococci, streptococci, and sometimes a few influenza bacilli. This group will be spoken of as the mixed infection group.

It is not my intention to assert that the findings in the sputum are proof that the organisms found are necessarily the cause of the disease. They may be considered as indicating the most probable cause, or at least, as giving the best obtainable evidence bearing on the cause, for purposes of comparison with the clinical manifestations. In 46 of these cases the clinical diagnosis was bronchopneumonia; in 2 cases it was lobar pneumonia followed by tuberculosis, without the lesion being specified as bronchopneumonia; in 5 cases no clinical diagnosis of any pulmonary condition was made.

The cases showed a great variety of clinical manifestations. In order to see if the differences in the clinical manifestations show any tendency to correspond with the above etiologic groups, I have analyzed them under the following headings:

1. Age.
2. Primary or secondary origin.
3. Rapidity of onset.
4. General condition of the patient.
5. Mental condition of the patient.
6. Presence or absence of cyanosis.
7. Character of the temperature curve.
8. Duration of illness.
9. Termination.
10. Physical signs in the chest.

In the first place, of the 29 cases in the mixed infection group, 5 may be differentiated from the others and set in a class by themselves. In these 5 cases no clinical diagnosis was made, the

diagnosis of bronchopneumonia being made only at autopsy. Although the bacteriologic examination showed a mixed infection, streptococci were especially predominant in all of these cases. I believe these cases represent a terminal infection not strictly to be classed as clinical bronchopneumonia. They occurred in children very sick with some other disease, were of sudden onset, great severity, brief duration, invariably fatal, and with slight or absent physical signs in the chest. To include them with the mixed infection group would, in view of their strikingly different and peculiar clinical manifestations, not give a fair picture of clinical bronchopneumonia, and I have therefore placed them in a separate class, which will be called the Terminal Infection Group.

Age.	Mixed.	Tubercular.	Influenza.	Pneumococcus.	Terminal.
2 yrs. or under,	100%	83%	28%	100%	60%
Over 2 yrs.,	0%	17%	72%	0%	40%

The only notable point in connection with the age is that in the influenza group the majority of cases occurred in children over two years of age while in the other three groups, the majority occurred in children under two years.

Origin. — All of the cases in the pneumococcus group were primary. Of the influenza cases, 3 followed whooping cough, the others being primary. Of the tubercular cases, 2 followed lobar pneumonia, the others showing no direct relation to any preceding disease. The majority of the cases of the mixed infection group appeared to be

secondary to some infection of the upper air passages, such as an ordinary cold, with gradual extension downward into bronchitis, and finally to bronchopneumonia. A certain number of them followed one of the recognized contagious diseases, such as whooping cough or measles, but the small number of such cases does not indicate that this is not a very common origin of bronchopneumonia, because such diseases are not admitted to the hospitals.

Onset.

	Mixed.	Tubercular.	Influenza.	Pneumococcus.	Terminal.
Gradual,	75%	59%	66%	0%	0%
Sudden,	25%	41%	33%	100%	100%

The percentage figures are not of very great significance as they are based on too small a number of cases, though they give a certain indication of difference in clinical type. The notable point is that in the pneumococcus group the onset was invariably sudden, whereas in the other three groups it was usually gradual. In two of the tubercular cases, classed as having a sudden onset, the disease began with typical lobar pneumonia, which was followed later by the finding of tubercular bronchopneumonia at autopsy.

General condition.

	Mixed.	Tubercular.	Influenza.	Pneumococcus.	Terminal.
Good,	17%	75%	57%	40%	0%
Poor,	83%	25%	43%	60%	100%

The figures represent the general condition when the patient was first seen. In the fatal cases it grew progressively worse. The notable

point is that the tubercular and influenza groups showed a good general condition in the majority of cases, whereas in the other groups this condition is reversed.

Mental condition.

	Mixed.	Tubercular.	Influenza.	Pneumococcus.	Terminal.
Unaffected,	21%	66%	86%	0%	0%
Apathetic,	42%	14%	100%	100%	0%
Semi-conscious,	26%	0%	0%	0%	0%
Unconscious,	10%	17%	0%	0%	100%

The differences in the mental condition presented, when the patients were first seen, were very striking, as the cases presented themselves clinically. The nervous system was strikingly unaffected in the tubercular and influenza groups, whereas it was affected in the majority of the cases of the other groups. The cases of the tubercular group in which it was affected presented themselves in the later stages of the disease.

Cyanosis.

	Mixed.	Tubercular.	Influenza.	Pneumococcus.	Terminal.
Present,	13%	41%	29%	20%	20%
Absent,	87%	59%	71%	80%	80%

There were no notable variations in the frequency of occurrence of cyanosis.

Temperature.

	Mixed.	Tubercular.	Influenza.	Pneumococcus.	Terminal.
High,	13%	17%	14%	100%	80%
Moderate or low,	87%	83%	86%	0%	20%

The differences found in the temperature curves, characteristic of the different groups, were among the most striking features of the analysis. The above figures represent the main characteristics

of the curves. In many of the cases with moderate course of fever, there were at times high exacerbations, while in some cases in which the fever was for the most part high, there were remissions. In general, the mixed infection, tubercular and influenza groups, showed a moderate course of fever, not often exceeding 102°, whereas the pneumococcus and terminal infection groups showed a course of high fever. The fever curves showed further characteristics. In the majority of the cases of the mixed infection group, the fever was moderate, with absolutely irregular exacerbations and remissions, ending by lysis in cases which recovered. The influenza group showed the same characteristics, but high exacerbations occurred more frequently, and the fever was in several cases extremely prolonged, ending by an exceedingly slow lysis. The tubercular group was characterized by regular remissions, and a wide daily variation between minimum and maximum temperature, so that the charts were often strikingly characteristic, although there were several marked exceptions. The pneumococcus group showed also very characteristic temperature charts, differing entirely from those of the other groups. The temperature was in general high, and steadily maintained, without marked remissions, and ended by an abrupt crisis, so that the charts often exactly resembled those of lobar pneumonia. In the terminal infection group, there was usually simply a brief high fever preceding death.

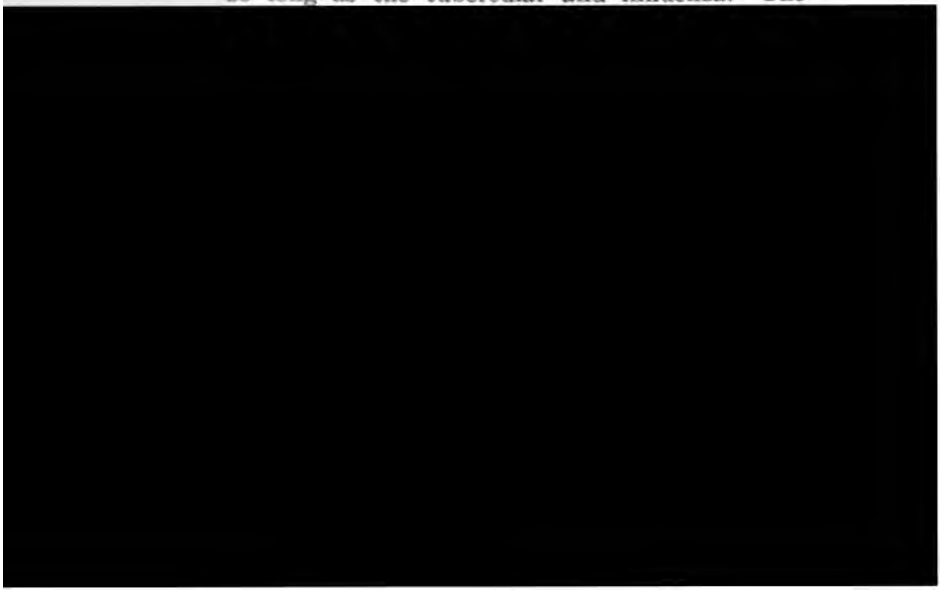
Rate of respiration. — The respiration was ac-

celerated to a varying degree in almost all cases. There was no relation between the rate of respiration and the etiologic group.

Duration.

	Mixed.	Tubercular.	Influenza.	Pneumococcus.	Terminal.
Under 1 wk.,	4%	0%	0%	60%	100%
„ 2 wks.,	37%	16% ?	14%	100%	100%
Over 2 wks.,	63%	84+%	86%	0%	0%
„ 3 „	37%	75+%	71%	0%	0%
„ 4 „	13%	42+%	71%	0%	0%
„ 6 „	0%	25+%	57%	0%	0%
„ 8 „	0%	0%	29%	0%	0%

The differences in the duration found in the different groups are very striking. The figures refer to the duration of the disease from the time of onset until either death occurred, or till the patient was free of symptoms and signs. It will be seen that the tubercular and influenza bronchopneumonias were of long duration, especially the influenza type, where most of the cases ran a course of many weeks. In striking contrast to these cases were the pneumococcus cases, in which the duration was quite brief in all cases. The duration of the mixed infection cases appeared very variable, being in general considerably longer than the purely pneumococcus infections, but not so long as the tubercular and influenza. The



cases of mixed infection, which I believe to represent terminal infections, showed a sharp clinical contrast in their very brief duration.

Here again there are striking differences in the different groups. The tubercular form is the more fatal, but the figures are of no value as bearing on the actual mortality of the various groups, because the studies were made upon selected cases, as many cases as possible which came to autopsy having been selected. Death also occurred in the large majority of the common mixed infection group, and when recovery occurred, the disease terminated by lysis. None of the influenza cases was fatal, and in all the termination was by lysis. The pneumococcus group presented a sharp contrast in that in all the cases which recovered, the disease terminated abruptly by crisis.

Physical signs in chest. — It is difficult to tabulate the physical signs found in a way which satisfactorily brings out the striking differences found in the various groups. There were a number of cases in which signs were more or less generally distributed throughout both lungs, the finding being crackling râles with or without consolidation, and there were cases in which the signs were confined to definite areas. Again, in some cases, only râles were found; in others, small areas of consolidation; in others, large areas of consolidation; and in a number of cases, numerous areas of consolidation appearing and disappearing successively.

	Mixed.	Tubercular.	Influenza.	Pneumococcus.	Terminal.
Diffuse signs,	100%	25%	0%	100%	40%
Localized signs,	0%	75%	100%	0%	0%
Diffuse râles only,	54%	8%	0%	80%	40%
Small areas of consolidation,	46%	8%	15%	20%	0%
Large areas of consolidation,	0%	84%	0%	0%	0%
Shifting areas of consolidation,	0%	0%	85%	0%	0%
Nothing abnormal found,	0%	0%	0%	0%	60%

It appeared that a diffuse distribution of the physical signs throughout the lungs is characteristic of the mixed infection and pneumococcus groups, and may occur in the tubercular group. Localization of the physical signs in definite areas is characteristic of the tubercular and influenza groups, especially of the latter. In the mixed infection and pneumococcus groups the most common finding was diffuse crackling râles only, without the detection of definite areas of consolidation being possible. When such areas occurred, they were usually small. In the tubercular and influenza groups, definite areas of consolidation were always found. In the tubercular group these areas were notably large, and strikingly persistent, the signs of consolidation persisting without much change over long periods of time. In the influenza group, while the areas of consolidation found were both large and small, they showed one characteristic peculiar to this group, in that they appeared and disappeared in succession. One or more areas of consolidation would appear, would last for a few days, and

then the signs of consolidation would vanish, leaving behind a lot of crackling râles localized in the same area, which in turn would disappear in a few days more. Meanwhile, from time to time, fresh areas of consolidation would appear and go through the same changes.

The above analysis suggests that there is a certain correspondence between the etiology, or at least the bacteriologic findings, in cover-glass preparations as representing probable etiology, and the clinical manifestations of bronchopneumonia. It thus becomes possible to subdivide the cases into fairly definite clinical types corresponding to the supposed etiology and to describe them separately. The points on which such a subdivision would be based are summarized in the following diagnostic table: [See table on page 114.]

Following the suggestions given by the comparison between clinical manifestations and etiology, the description of bronchopneumonia would be as follows, including only peculiar features, not symptoms common to all forms.

Bronchopneumonia may be divided into the following types:

1. The commonest type, including most of the cases of so-called secondary bronchopneumonia, which is probably caused by mixed infection, and is a disease principally of the first two years of life. It usually follows either one of the recognized specific infections, or upon an infection of the higher air passages, extending downward into bronchitis, and then into bronchopneu-

	Age.	Onset.	Mental condition.	Temperature.	Duration.	Termination.	Signs in chest.	Sputum at at autopsy.
Mixed	Infants	Gradual	Affected	Moderate	Medium	Death or lysis	Diffuse	Mixed Infec.
Tuber.	,,	,,	Clear	,,	Long	Death	Localized	Tuber. Bac.
Influenza	Children	,,	,,	,,	Very long	Lysis	Shifting	Infl. Bac.
Pneumococcus	Infants	Sudden	Affected	High	Short	Crisis	Localized	Pneumococcus
Terminal	All ages	,,	,,	,,	Very short	Death	Diffuse or none	Mixed-Streptococci ?

monia. The onset is usually gradual, the general condition is usually much impaired, being serious from the start, and the nervous system is often notably affected. The temperature is usually moderate, with irregular exacerbations and remissions. The duration varies, being about one to five weeks. The prognosis is very serious, a great many cases ending fatally. Those cases which recover terminate by lysis. The principal physical sign in the chest is the presence of diffuse, fine, moist râles, having a peculiar crackling quality, and sounding close to the ear. In many cases this is the only sign, while in other cases small areas of consolidation appear in various parts of the lungs. The sputum shows a variety of micro-organisms, and post-mortem examination shows a typical general bronchopneumonia.

2. *Tubercular bronchopneumonia* which is probably second in frequency. It is a disease principally of infancy, though it may occur in older children. My observations lead me to believe that when it occurs in older children, it is usually secondary to some other form of pneumonia. The onset is usually gradual, and the general condition, while it may be serious from the start, is usually good at the beginning, becoming progressively worse. The nervous system is strikingly unaffected during the greater part of the illness, the children often taking a marked interest in their surroundings, even after their general condition becomes serious. The temperature is variable, usually moderate,

with a tendency to marked remissions, which usually occur in the morning, but which may occur in the evening, the chart often showing a very characteristic up-and-down curve. The duration is long, about two to six weeks, or even more. The prognosis is very bad. None of the cases in this series recovered, two being discharged not relieved. I believe, however, from cases which I have seen but have not been able to prove tubercular, that recovery is possible. The most characteristic physical sign in the chest is the gradual appearance of rather large areas of consolidation which persist for a long time. The areas may be small, and there may be diffuse crackling râles generally distributed, so that the physical signs may be exactly the same as those seen in the common bronchopneumonias of the preceding type. Tubercle bacilli are often difficult to find in the sputum. At autopsy is found the characteristic caseous pneumonia.

This form of bronchopneumonia is to be distinguished from the common mixed infection form, by the clear mental condition of the patient, by the tendency toward localized large and persistent areas of consolidation in the chest, and more than all by the peculiarities of its temperature curve. Nevertheless, it is often very difficult to make the diagnosis, particularly when the temperature curve is not characteristic, and when the signs in the chest are diffuse.

3. *Influenza bronchopneumonia*, which is not common, except when influenza is generally prev-

alent. It is a disease principally of childhood and adult life rather than of infancy. It usually follows an influenzal infection of the higher air passages, which finally involves the lungs. The onset may be sudden in the first place, but the symptoms of pneumonia usually come on gradually. The general condition is often serious at the start, but may be good. The nervous system, in children at least, is usually but little affected. The temperature is irregular, for the most part moderate, but with a tendency toward high exacerbations which last from a few hours to several days. Fever is very prolonged, the temperature returning very gradually to the normal. The entire duration of the illness is strikingly long, about 2 to 8 weeks. The prognosis is good, complete recovery being the usual termination. The signs in the chest commonly do not involve all parts of the lungs at once, and diffuse crackling râles are not found. Recognizable areas of consolidation occur successively in various parts of both lungs, persisting only for a few days, and then disappearing, leaving in their place a collection of râles. This shifting appears to be quite characteristic, and can best be understood from the illustrative case given below. Influenza bacilli, both within and without the leucocytes, are found in great numbers in the sputum, which is very purulent in character. I have seen no autopsies of this type.

This form of bronchopneumonia is to be distinguished from the common secondary form by

its occurrence later in life, by its generally less serious nature, by the less common affection of the nervous system, by its prolonged duration, and more than all by the peculiarities of the physical signs found in the chest. It is to be distinguished from the tubercular form by the differences in the temperature curves, by the tendency to become progressively better, and by the shifting character of the signs in the chest.

4. *Primary pneumococcus bronchopneumonia.* — This is essentially a disease of the first two years of life. Both its clinical aspect and the findings in the sputum suggest that it is caused by an infection of the pneumococcus only. Like lobar pneumonia, it occurs in well patients, and the onset is sudden. The nervous system is usually affected to some extent, as in lobar pneumonia. The temperature rises rapidly, is high and steadily maintained, and falls by an abrupt crisis. The duration is short, resembling lobar pneumonia. The prognosis is much more favorable than in the common secondary bronchopneumonias. Convalescence is rapid. The physical signs in the chest are diffuse, consisting of crackling râles, with or without small areas of consolidation, and exactly resembling the signs found in the mixed infection type. The sputum resembles that of lobar pneumonia, being tenacious, not purulent, and containing few organisms except the pneumococci, which are found both within and without the leucocytes. At autopsy the lesions resemble those of the common secondary type.

This form is to be distinguished from the preceding forms by its abrupt onset, high sustained temperature, and termination by crisis. It may be distinguished from lobar pneumonia from the fact that from the start it presents diffusely distributed physical signs.

5. *Terminal bronchopneumonia.* — This form may occur at all ages. It is represented by the rise of temperature, pulse and respiration, which so often occurs as the end picture of various diseases. In such cases a fresh acute bronchopneumonia is found at autopsy. There are sometimes no physical signs found in the chest, or there may be diffuse râles. It is distinguished from the preceding types by its occurrence in the course of some other disease, at a time when the patient's general condition is poor and by the absence of definite clinical characteristics.

The above description represents only typical cases. In practice, cases which conform absolutely to the type are infrequently met with, as every sort of variation may occur. It is notable that in this series the correspondence between etiological type and clinical picture was by no means constant, for in all the groups exceptions occurred where such correspondence was lacking, and where cases belonging to one etiological group presented to a greater or lesser extent the clinical features of another. Nevertheless, similar exceptions occur in most other diseases. In order to determine how far the exceptions would render inaccurate diagnoses based on the diagnostic

scheme outlined above, I have taken the same series of cases from a purely clinical point of view, basing the diagnosis of each case upon the clinical data as presented in the first five days of observation, and then comparing the results with the sputum and autopsy findings.

Of the group of mixed infections, in 17 the diagnosis was correct, while in 7 the diagnosis was mixed infection or primary pneumococcus; the only point in favor of the latter being a sudden onset and temporary high temperature. Of the tubercular cases, in 6 the diagnosis was correct, in 3 it was tubercular or mixed infection, in 1 it was tubercular or influenza infection, and in 1, with a sudden onset and high temperature at the start, it was primary pneumococcus infection. In 5 of the influenza cases a correct diagnosis was made, as in them the shifting character of the signs was apparent by the fifth day; 2 cases might be mistaken for the tubercular form. Of the primary pneumococcus cases, 4 were typical and easy to recognize, while in the fifth the diagnosis was pneumococcus or mixed infection. Of the terminal infections, in 3 the diagnosis might possibly have been made correctly.

I believe this division of the bronchopneumonias into etiologic types, each having certain clinical features by which it may be recognized, though necessarily limited in its practical application, will nevertheless enable the physician in very many cases to make a diagnosis which will describe much more closely the real condition

present than if it were simply bronchopneumonia without the type being specified. Such a diagnosis, reaching beyond the lesion as far as the probable cause, should be of much greater value in the practical aspects of prognosis and treatment.

The following are illustrative cases of the various groups.

1. *Mixed infection group.* — Joseph M. Doucett, one year old, was admitted to the Children's Hospital, on March 27, 1903. He had had a cough for some time, and the parents had been told by a physician that he had bronchitis. Three days ago he began to seem sicker, began to cough more, and was noticed to be feverish. His breathing has gradually become more rapid. On admission the respiration was found to be accelerated, and the general condition was poor. The child was conscious but apathetic. Medium and fine crackling râles were found throughout the chest, but there was no dullness nor modification of the respiratory murmur.

On March 29, an area the size of a 25-cent piece appeared just outside the left nipple, over which there was dullness and broncho-vesicular breathing.

On April 2, there was in addition a varying degree of broncho-vesicular breathing throughout the chest.

April 4, the child seemed to be improving. The physical signs were unchanged. From this time the general conditions became progressively worse, and the patient died on April 17. [See Chart I, page 122.]

2. *Mixed infection.* — James Henry Davis, two months old, colored, was admitted to the hospital on Oct. 22, 1906. Has had a bad cold with cough and vomiting for several days. No fever has been noted.

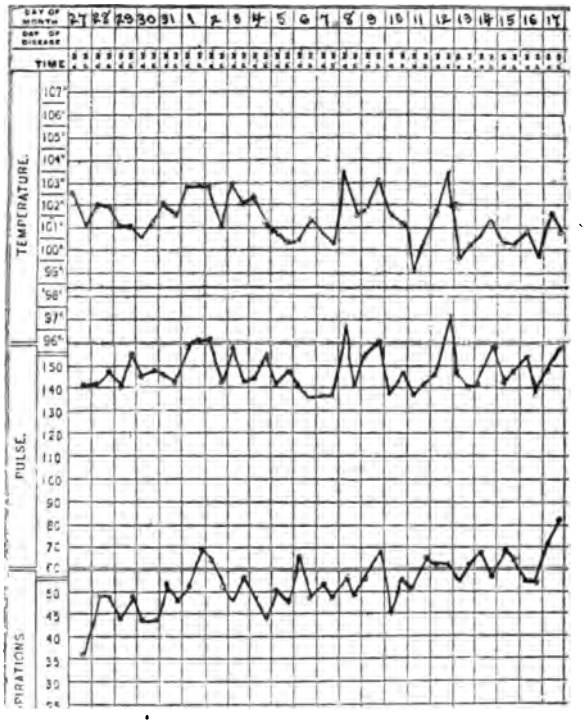


CHART I. MIXED INFECTION.

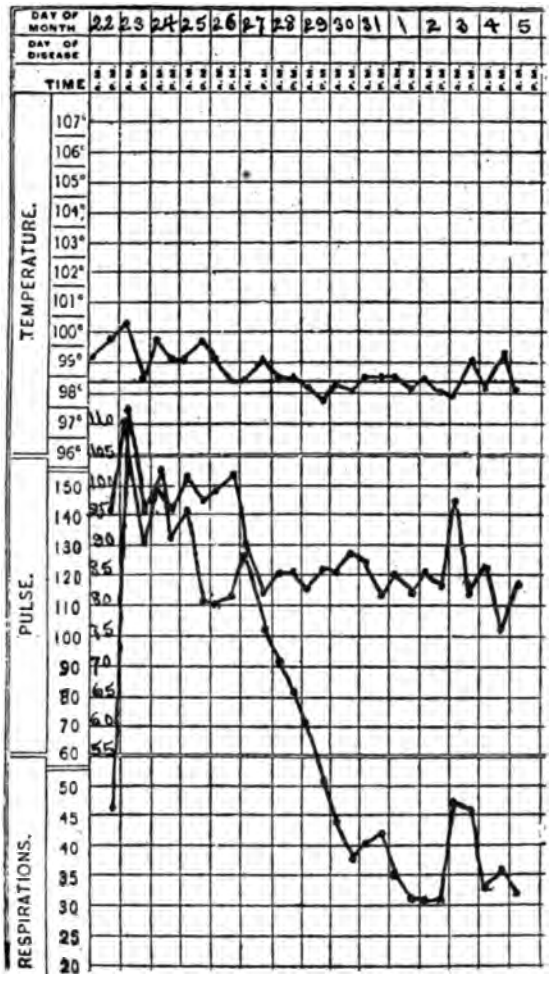


CHART II. MIXED INFECTION.

On admission the respiration was accelerated, the general condition very poor, mental condition apathetic. Numerous medium and fine crackling râles were heard throughout the chest. The temperature was only 99°. On the following day, the pulse went up to 170, and the respiration became extremely accelerated, 110 to the minute. There was no notable rise of temperature.

From this time on the patient improved steadily, and on April 5 was discharged with a few coarse râles in the lungs. There were never any clinical signs of consolidation. [See Chart II, page 123.]

3. *Tubercular bronchopneumonia.* — Hazen Goodwin, eleven months old, was admitted to the Infants' Hospital Jan. 14, 1905. He had had a cough for some time, but the onset of symptoms had been gradual, and the history was unsatisfactory. Physical examination showed an emaciated infant. He took food well, and noticed his surroundings. The respiration was accelerated. There was dullness over both the lower and upper lobes posteriorly on the right, with bronchial breathing and crackling râles. On Jan. 20, the same signs were present on the right, and there were crackling râles in the left upper lobes in front. Tubercle bacilli were found in the sputum.

The signs persisted till the patient's death on Jan. 25. [See Chart III, page 125.]

4. *Tubercular bronchopneumonia.* — Elsie Forskind, six months old, was admitted to the Children's Hospital March 18, 1904. She had had a cough for some time and had gradually become sicker and more feverish. There was slight dullness near the left anterior axillary line, with coarse moist râles.

March 24, there was dullness throughout the left axilla, with bronchial breathing, and fine moist râles, and

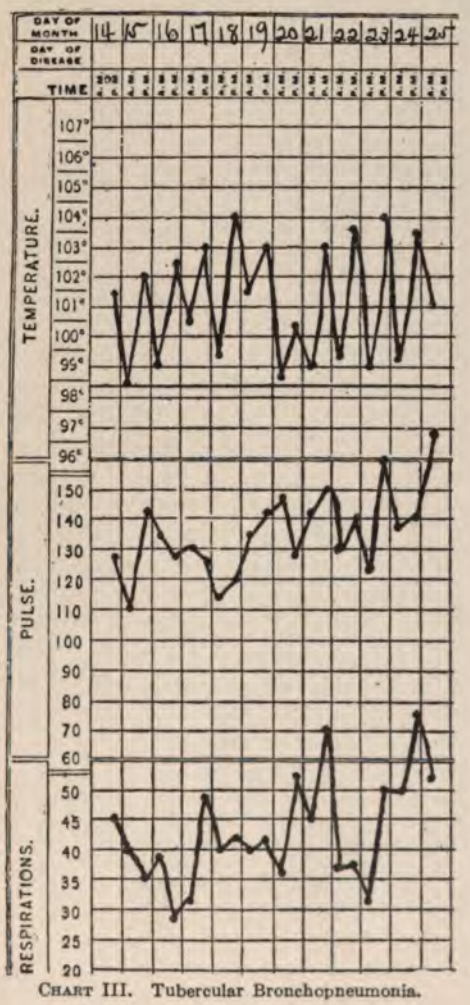


CHART III. Tubercular Bronchopneumonia.

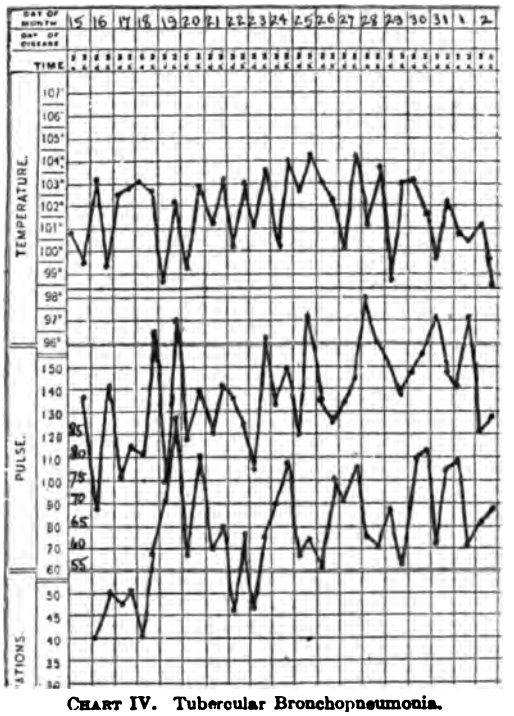


CHART IV. Tubercular Bronchopneumonia.

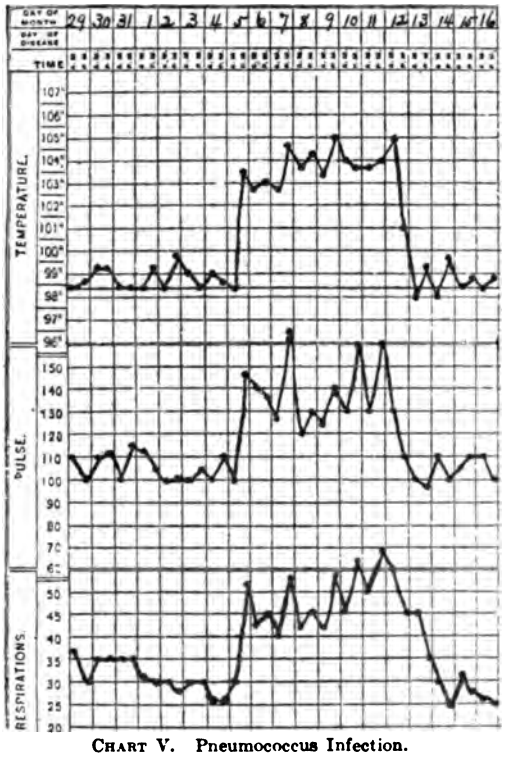


CHART V. Pneumococcus Infection.

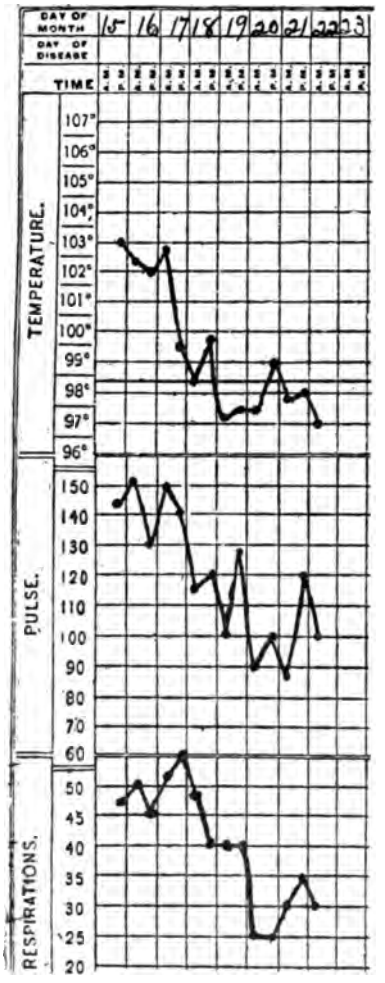


CHART VI. Pneumococcus Infection.

slight dullness appeared in the middle of the right back, with bronchial breathing and moist râles.

March 30, marked cyanosis appeared. The signs remained unchanged, except that the dullness in the left axilla had spread posteriorly.

April 1, the dullness had spread further over the front of the left chest.

April 3, died. Autopsy showed caseous pneumonia throughout both lungs. [See Chart IV, page 126.]

5. *Primary pneumococcus bronchopneumonia.* — Charlotte McHugh, two years old, had been treated for indigestion, and was under observation when the present illness occurred. On Feb. 5, 1903, she suddenly became very feverish, with cough and rapid breathing. Numerous fine crackling râles were found scattered throughout the chest, and the respiration became accelerated.

Feb. 8, a small area of dullness and bronchial breathing appeared in the right back at the level of the sixth rib.

Feb 10, a similar area appeared on the left, near the anterior axillary line.

Feb. 12, an abrupt crisis occurred, which was rapidly followed by disappearance of all signs. [See Chart V, Page 127.]

6. *Primary pneumococcus bronchopneumonia.* — Alfred Conroy, twenty-two months old, was admitted to the Infants' Hospital Oct. 15, 1907. Three days previously he became feverish, began to cough and seemed quite sick. On admission the general condition was poor, the expression dull and distressed, and the respiration accelerated. Numerous fine and medium crackling râles and a few dry râles were found throughout the chest. There was a critical fall of temperature on Oct. 17, followed by rapid disappearance of the râles. [See Chart VI, page 128.]

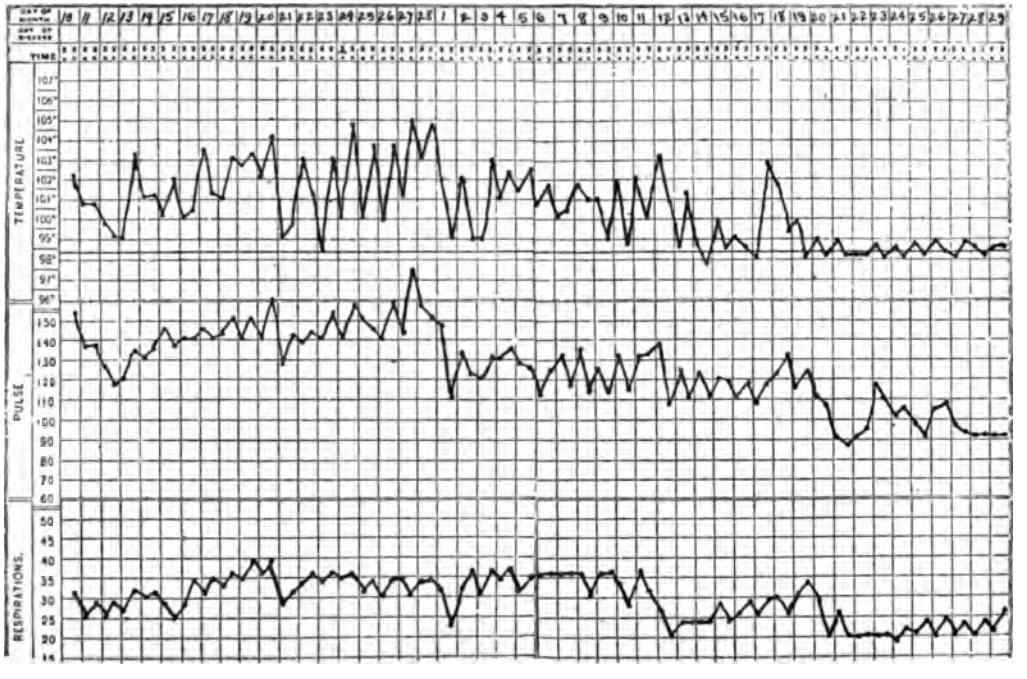


CHART VII. Influenza Bronchopneumonia.

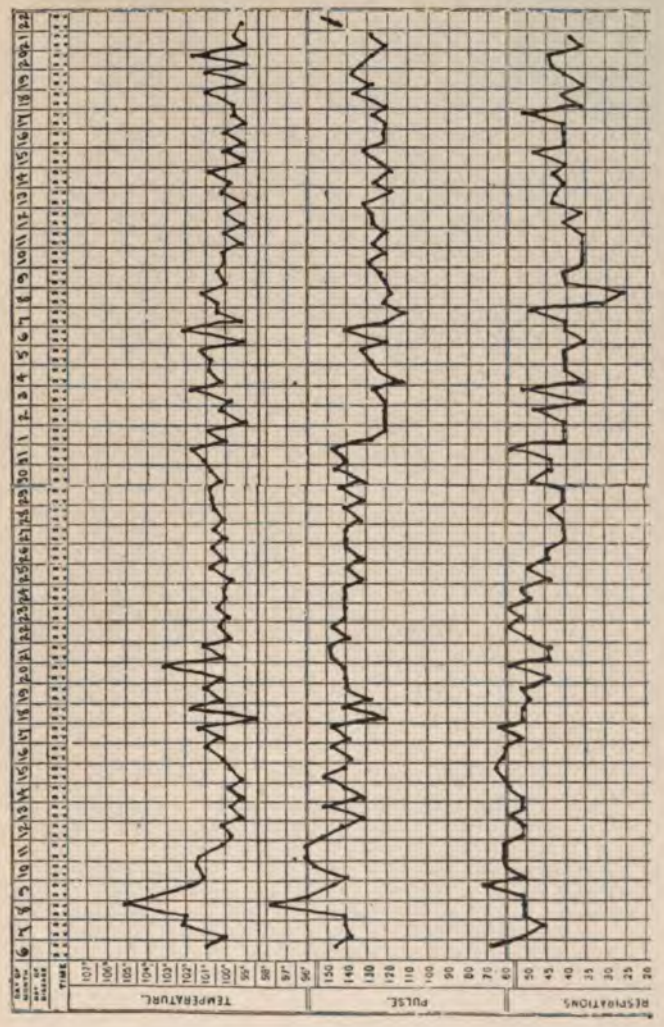


CHART VIII. INFLUENZA BRONCHOPNEUMONIA.

7. *Influenza bronchopneumonia.* — Florence Thompson, two years old, was admitted to the Children's Hospital Feb. 10, 1903. Two weeks previously she began to have a short, dry cough. Four days ago fever was noted, but the respiration was not accelerated.

On admission, the general condition was good, and the mind clear. In the lower part of the left lobe behind was a small area of dullness, with coarse moist râles. There were a few moist râles in various other parts of the lungs. Influenza bacilli were found in great numbers in the sputum.

Feb. 14, the patch of dullness in the left back had disappeared, and was replaced by a collection of fine moist râles. A patch of dullness with bronchial breathing appeared in the right back near the spine.

Feb. 17. The signs of consolidation near the spine on the right back had disappeared, being replaced by a collection of medium moist râles.

Feb. 22. No notable change.

Feb. 28. An area of dullness has appeared under the angle of the right scapula, with bronchial breathing and crackling râles. Child is very apathetic.

March 9. The signs of consolidation have disappeared, being replaced by a collection of medium moist râles.

March 9. Child is very apathetic; seems to be failing rapidly. Many râles in localized areas in both lungs.

March 23. Improvement for last three days. This continued steadily, and the patient was discharged relieved on April 1. [See Chart VII, page 130.]

The other cases of influenza bronchopneumonia were similar to the above. [See Charts VIII and IX, pages 131 and 133.]

8. *Terminal infection.* — William McDonald, eleven years, was admitted to the Children's Hospital May 22,

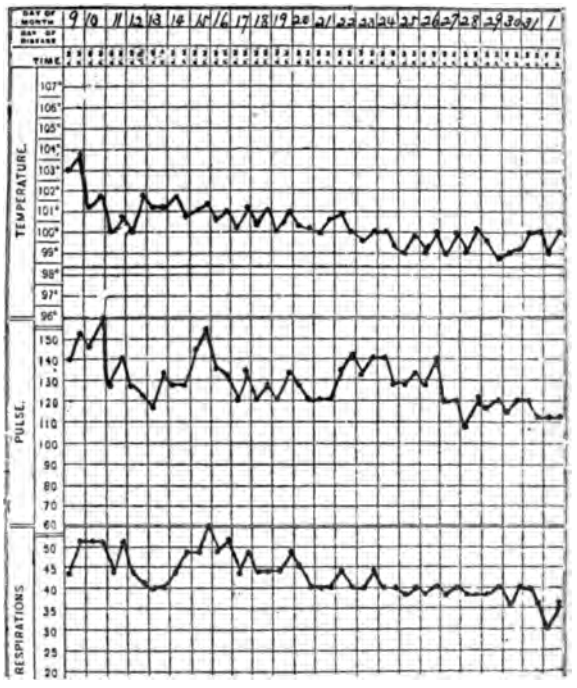


CHART IX. INFLUENZA BRONCHOPNEUMONIA.

1907, with tubercular meningitis of ten days' duration. In the last twenty-four hours the respiration became very rapid and the temperature rose before death, and acute bronchopneumonia was found at autopsy, and cover-glass preparations from the lungs showed pneumococci and many streptococci.

THE DIAGNOSIS OF CIRCULATORY CONDITIONS BY TEMPERATURE MEASUREMENTS.

BY THEODORE JEWETT EASTMAN, M.D., BOSTON,
Medical House Pupil, Massachusetts General Hospital, 1907.

ATTENTION has long been paid by physiologists to measurements of the temperature of the skin in various parts of the body under varying degrees of warmth of the surrounding air; and the effect of exercise on the superficial temperature has been studied, particularly by Kunkel.[1] No observations, however, so far as I can find, have been published regarding the relation of body temperature to that of the extremities in disease.

This question was suggested to me by Privat Docent Dr. Ludwig Braun, of Vienna, to whom I take this opportunity of expressing my gratitude for his constant aid and suggestion during the course of my investigation. I wish also to express my thanks to Primarius Dr. Ritter von Frisch, through whose kindness I was enabled to carry on the work in his Abteilung in the K. K. Allgemeines Krankenhaus, in Vienna, and to his assistant, Dr. Hawdek, for many kindnesses.

When we measure the temperature of the skin in different parts of our extremities, we find that the nearer to the heart we measure, the higher the temperature. Davy,[2] using a mercury ther-

mometer, found that, with a room temperature of 20° C.,* the temperature of the sole of the foot was 32.2° over the rectus femoris, 32.78°, and in the inguinal fold, 35.84°; and Kunkel,[3] using the more accurate thermo-electric measurement apparatus, found at the same room temperature the following values: dorsum of hand, 32.5° to 33.2°, forearm 33.7°, upper arm 34.3°, calf of leg 33.6°, thigh 34.2°.

The temperature of a part is dependent upon its chemical heat production, and upon the quantity of blood flowing through the part in a unit of time; that is, upon the rate of flow of the blood. Since the chemical heat production in the extremities in a state of muscle-rest is of extremely slight importance, the above mentioned differences in temperature can be caused only by the cooling which the blood undergoes on its way from the heart to the periphery. The farther a part is from the axis of the body, the lower its temperature.

It is, from the physiological point of view, of great interest that from the temperature of the skin surface we can judge of the circulation in the underlying tissues, although, as we shall see later, in varying degree in different parts of the body. In this regard, Tigerstedt[4] says: "The metabolism of the skin is slight, and the warmth of the skin is therefore derived principally from the heat radiated to it directly, particularly from the blood flowing in the deeper vessels. The greater the

* Throughout this article the temperature used is Centigrade.

quantity of this blood. the warmer the skin. During its circulation through the cutaneous vessels, the blood is cooled, and the quantity of heat radiated to the surrounding tissues must be in direct proportion to the amount of blood supplied."

Klapp [5] has shown that hyperemia artificially produced on the surface of the body extended even to the viscera, and from this we must assume the presence of hyperemia in the deep portions of a limb when we find an increase in its surface temperature,[6] and Bier [7] shows that even a moderate degree of passive congestion is not confined to the skin, but extends even into the bone-marrow, and says further: " In deep-lying inflammatory processes the skin contains much more blood than it normally does; such is the case even with the skin of the abdominal wall in deep inflammations."

O. Müller [8] found that cold diminishes the volume of the forearm, heat slowly increases it, and also causes it slowly to diminish.

Finally, we find the same idea in an article by Exner [9] who says: " For the understanding of the phenomenon of erection, it is important to note the very striking increase of temperature of the penis. Wherever we observe in the body of a warm-blooded animal such a rise in temperature, it means, in the first place, an increase in the amount of blood which enters the organ in a unit of time. There is no reason to believe — indeed, under the existing anatomical relations it is very

unlikely — that the increase in the blood supply takes place simply in the skin of the penis; rather does a greater quantity of blood flow through the entire penis during erection than during relaxation. Since also the rise in temperature of the penis remains unchanged during a long-continued erection, it cannot be explained by the blood which flowed into the penis at the beginning of the erection, for this would in a few minutes become cooled, just as a finger, in which blood has been collected and retained by means of a tourniquet soon becomes cooler. The lasting rise in temperature during a long-continued erection shows that more, and presumably much more, blood per second flows through the penis then than when it is in a condition of relaxation."

It is then evident that by measuring the temperature of the skin in any place on a limb we can to a certain degree inform ourselves regarding the blood-content of the extremity, or, at least, of that particular portion (cross section) lying beneath the place of measurement.

The following investigations were made in order to find if possible whether, by temperature measurements on the body surface, one could gain information regarding the rapidity of flow of the blood under some pathological conditions of the circulatory apparatus, and thus obtain some light upon this important question. B. Lewy says [10]: "The rate of flow of the blood is the best indicator of the condition of the circulatory apparatus, for upon the amount of blood flowing through the

aorta in a unit of time depends the quantity of oxygen and of nutrient material carried to the periphery, if we disregard the respiration and absorption."

It is but natural to think that by measurements, such as the above mentioned, one could gain information only regarding the blood-content of the periphery, but our results show that the method is of value in judging the whole circulation and the cardiac condition as well.

The work was begun on normal persons and on patients suffering from heart lesions, the temperature measurements being at first made in the axilla (as is the usual custom in the Vienna hospitals) and in the closed hand, but it was soon found that the axillary measurements were unreliable, and so this method and the figures obtained by it were discarded, and all further measurements were made in the rectum and in the closed hand.

Some observers have used mercury thermometers in measuring superficial temperatures, the flattened bulbs, coils, etc., being applied to flat surfaces, but this method is open to the objection that the temperature of the surrounding air cannot be prevented from exercising an influence on the result. Kunkel[11] used an electrometer with two contact points a few millimeters in diameter which he applied to the skin under conditions of good insulation, but the measurement of such a small surface seems to me unreliable.

To avoid as far as possible these objections my

measurements were made with special thermometers with a cylindrical bulb 4.5 cm. long and 1.0 cm. in diameter, a size conveniently grasped in the hand, and presenting a large surface to the skin. This thermometer was laid in the palm of the hand and the fingers closed lightly over it, and then the fist and wrist were thickly and not too tightly bound up in several layers of thick sheet wadding, to exclude as far as possible the outer air and to prevent evaporation of perspiration and a resultant lowering of temperature. After many experiments it was found that the maximum temperature in the hand was reached in about twenty minutes, but nearly all measurements were made during thirty-five to fifty minutes for the sake of certainty.

To keep as nearly constant as possible the effect of digestion on the distribution and temperature of the blood [12] the measurements were made at the same time daily, and to rule out as much as possible the effect of the muscular exertion [13] the patients were required to lie well covered up in bed for an hour before the measurements were made, and to remain in bed during the measurements, except in the case of the exercise experiments.

The patients whom we regarded as " normal " for our purposes were those ambulatory convalescents so much more numerous in Vienna hospitals than in ours, who had slight gastric catarrh, convalescents after slight attacks of tonsillitis, a patient with a dislocated semilunar cartilage, a

scar at one apex and slight emphysema, a patient with a moderate degree of chlorosis and a patient perfectly recovered from gas-poisoning. In all cases were the patients without fever, for it was found that the temperature relations in febrile cases were too complicated to be clinically useful, and in no case was arteriosclerosis clinically determinable. In practically every case at least ten measurements were made, and in many cases twenty, but in either case the averages were practically identical.

Our first measurements were made with the purpose of finding out whether the temperature difference in health and in cases of cardiac insufficiency was a true one, since most patients with insufficiency have cool hands and feet, and, frequently and on slight provocation, complain of cold.

It should be noted that before making the measurements the patients' hands were warmed by being kept beneath the bedclothes, as mentioned above, and the patients with vasomotor neuroses, whose extremities are frequently livid or " marbled " and cold, were not used in these estimations. These patients have temperature differences between hand and rectum, sometimes as great as 4°, and we avoided, by thorough investigation of the heart and the nervous system, the mistake of regarding these differences as evidence of an organic circulatory disturbance. The results obtained are naturally not to be considered as illustrating a diagnostic method com-

plete in itself, but rather only as a part of the whole clinical procedure, in the same way that measurement of the body temperature (axillary, rectal or oral) in febrile cases is only a part of our routine examination.

The action of the circulation, especially of the vasomotors, is so extremely complicated and variable, and to such a degree reciprocal, that we can scarcely expect to determine an exact, fixed relation between the variations in the circulation of central (cardiac) origin, and the temperature differences.

In 350 measurements made in rectum and hand as described above, the following facts were presented:

The differences between rectal and hand temperatures in normal individuals varied from 0.6° to 1.3°, and in rare instances to 1.5°.

The value of these averages may be shown by quoting the variations in some cases taken at random:

A mild chlorosis, in which the temperature differences between rectum and hand were, in ten measurements, eight times less than 1°, once 1° and once 1.45°.

The recovered case of gas-poisoning in ten measurements, five times less than 1°, four times less than 1.5°, and only once 2.5°, in which case the hands were noticeably very cold before the measurement was made.

A case of slight gastric catarrh, in ten measurements, nine times less than 1°, and once 1°.

A similar case, in seven measurements † four times less than 1°, the other three, 1.1°, 1.2° and 1.5°.

Case of slight emphysema, in twenty measurements eight times less than 1°, ten times between 1° and 1.5°, once 1.9°, and once — hands very cold — 2.1°.

We turn now to figures obtained in cases of various forms and grades of cardiac insufficiency, primary and secondary.

Thus, 2 cases of nephritis with much edema and cardiac insufficiency showed differences between rectal and hand temperatures of from 1.8° to 3.4°. The large differences of more than 2° (even after an hour's measurement in the hand) were, in one of these cases, found in ten measurements nine times, and twice the difference was more than 3°. In the second case there was found, in twenty measurements, fourteen times a difference of more than 2°, and of these, six were of 3° and more.

One of these patients showed at one time a decided improvement, with increased diuresis and a diminished absolute albumin excretion; and during this time differences of 1.25°, 1.1°, 1.05° and 1° were found, while at a time when the opposite conditions prevailed the consecutive differences found were 3.2°, 2.0°, 2.3°, 1.5°, 2.8°, 1.6°, 2.9°, 3.4°, 2.7° and 3.4°.

In contrast to these cases a case of subacute nephritis without any symptoms of cardiac insufficiency showed in seven measurements, six under

† Patient " discharged well " before our series was finished.

1°, and only once as high as 1.1°, showing that it is cardiac insufficiency and not the nephritis (with easily determinable edema of the skin) which causes the large temperature differences.

In a fever-free case of acute endo-myo-pericarditis with hydrothorax, ascites, and edema of the feet and lower legs, were found in twenty measurements, six times a difference of 3° and over, seven times more than 2°, and three times 1.8°, the other differences being 1°, 0.9°, 0.8°, and 0.65°. At the same time the twenty-four-hour amount of urine varied from 400 ccm. to 2,500 ccm., the highest diuresis taking place on the days when the temperature differences were least, and *vice versa*.

We turn now to the findings in cases of chronic cardiac insufficiency of various sorts — simple and multiple valvular lesions, as well as myocardial affections.

1. Mitral stenosis and insufficiency, slight aortic insufficiency, twenty-two measurements:

12 differences of more than 2°, of which 2 were 2.9°.
4 „ „ „ „ 1.8°
3 „ „ 1.7°
The others 1.1°, 1.0°, 0.7°

2. Same diagnosis, but patient not as well as the preceding one; ten measurements:

3 differences of 3° and over
4 „ „ 2° „ „
2 „ „ 1.6°
1 difference „ 1°

3. The same diagnosis, eight measurements:

5 differences of more than 2°
2 „ „ 1.8°
1 difference „ 0.9

In contrast to these figures, a case of pure aortic insufficiency showed in ten measurements: nine differences of less than 1° and only one difference of 1°.

This result is undoubtedly to be accounted for by the dilatation of all the vessels (shown by increased pulse volume, marked increase in the difference between systolic and diastolic blood pressure, and flabby vessels) which is peculiar to this heart lesion.

We find then: *in cardiac insufficiency (except pure aortic insufficiency) greater temperature differences than under normal conditions.*

Finally, we determined, by means of muscular exertion carried to the limit of endurance, the effect upon the temperature differences of exhaustion with a normal heart and in cases of cardiac disease. For this purpose, after ascertaining my rectal temperature, diastolic and systolic blood pressure ‡ and pulse rate and having held a delicately reacting thermometer in my bound-up fist until a constant temperature was reached, I exercised as vigorously and rapidly as possible with an 8 kg. iron weight held in the free hand, using not only the arm in the exercise, but bending the knees and back also, in order to produce fatigue in general, and not in the muscles of the arm alone. The temperature in the hand was noted during the exercise, and as soon as I was obliged to stop on account of exhaustion and inability to carry it further the above mentioned measurements were repeated. The results obtained are shown in the following tables:

‡ Riva-Rocci instrument.

Dec. 18.

Time.	Rectal temperature.	Hand temperature.	Blood pressure.	Pulse rate.
11:10	37.4°	34.4°	Sys. 110 / Diast. 83	88
11:30		35.1°		120
11:35		36.0°	Sys. 120 / Diast. 90	
11:40		36.2°		90
11:50	37.5°	36.2°		

Exercise began at 11:15
„ ended at 11:35

Dec. 30.

Time.	Rectal temperature.	Hand temperature.	Blood pressure.	Pulse rate.
3:45	37.5°	34.1°	Sys. 115 / Diast. 85	94
3:50		34.8°		129
3:55		35.6°		132
3:58	37.5°	36.6°	Sys. 120 / Diast. 92	128
4:05		36.5°		
4:10		36.5°		100

Exercise began, 3:45
„ ended, 3:58

Jan. 29.

Time.	Rectal temperature.	Hand temperature.	Blood pressure.	Pulse rate.
6:50	37.4°	33.9°	Sys. 115 / Diast. 90	80
6:58		35.0°		129
7:02		35.9°	Sys. 125 / Diast. 98	135
7:07	37.6°	36.2°		
7:12		36.4°		86

Exercise began, 6:50
„ ended, 7:02

We see here that the temperatures in the rectum are practically unchanged, whereas the temperature in the hand rose in the first experiment 1.8°, and in the other two, 2.5°. That these rises in temperature are not due to a rise in blood temperature, but simply to a greater amount of blood at body temperature sent to the periphery,

is shown by the practically unchanged rectal temperature.

Vastly different were the results obtained in 2 cases of cardiac disease of such a degree that the patients were comfortable only when exercise was avoided. In these patients moderate exertion (walking up and down the ward a few times) was sufficient to produce severe fatigue, increase of the cardiac arrhythmia, palpitation, cyanosis, and marked depression of spirits. The patients, it may be said, were intelligent, were thoroughly interested in the experiments, and assented gladly to repeated performances of them.

In order to keep as uniform as possible the conditions under which these experiments were made, the patients remained in bed for two days before the experiments were begun, and during the days of the experiments, getting up only for the exercise to be mentioned, and during all these days they received the same diet.

For the test, the patient's rectal temperature and that of the hand were taken, the patient being in bed. The patient then walked up and down the ward until exhausted, the quickly-registering thermometer remaining in the bound-up hand all the time. When exhausted the patient's rectal temperature was again measured.

The investigations on these patients gave results which agree in both cases, and in which there is little room for doubt, as in each case the measurements were made four times. They showed that the rectal temperatures in each case remained

unchanged by the exercise or showed only a very slight rise or fall; whereas the temperature of the hand in the first case showed a drop of 1.9°, 1.6°, 1.25° and 1.2°, and in the second case, drops of 1.2°, 0.8°, 2.5° and 0.4°.

This is shown more fully in the following tables:

I. Kop.

Moderate degree of cardiac insufficiency without edema.

Date.	Rectal temperature.	Hand temperature.	
Dec. 19			
A.M.	37°	35.2°	Before exercise
	36.9°	33.3°	After ,,
P.M.	37.4°	34.9°	Before ,,
	37.5°	33.6°	After ,,
Dec. 20.			
A.M.	36.8°	34.85°	Before exercise
	36.8°	33.6°	After ,,
P.M.	36.8°	35.7°	Before ,,
	36.8°	34.5°	After ,,

II. Bl.

Greater degree of insufficiency, slight edema, dyspnea.

Date.	Rectal temperature.	Hand temperature.	
Dec. 19			
A.M.	36.9°	35.1°	Before exercise
	36.5°	33.9°	After ,,
P.M.	37°	35.8°	Before ,,
	37.25°	34.9°	After ,,
Dec. 20.			
A.M.	37°	34.3°	Before ,,
	37°	31.8°	After ,,
P.M.	37.4°	36°	Before ,,
	37.4°	35.6°	After ,,

Patients with cardiac insufficiency show, then, after physical exertion, which in such cases, on account of the diminished reserve strength, can only be slight, no diminution, but often on the other hand marked *increase* in the temperature

difference between rectum and hand as evidence of the insufficiency of the affected heart, for the cooling of the extremities means nothing other than an insufficiency of the circulation; that is to say, a diminution in the blood supply to the part in question.

Since this reaction seems to increase with the severity of the cardiac insufficiency, we may, other things being equal, determine from the temperature differences the degree of cardiac impairment present, either with the patient at rest or after exercise.

Finally, to show the effects upon the circulation of treatment of a broken compensation, the following case is quoted. The measurements were made morning and afternoon from the day of entrance until the day of discharge (with recovered compensation) and prove the recognized fact that improvement in the cardiac power results in an improvement in the peripheral circulation. The patient was given digitalis beginning after the first measurement, and was kept quiet in bed.

STEIN, AGE 34.

Mitral stenosis and insufficiency. Broken compensation.

Meas.	Rectal temperature.	Hand temperature.	Difference.	Duration of measurement.
I	37.2°	33.8°	3.4°	35 minutes
II	37.7°	34.7°	3°	35 "
III	37.2°	34.2°	3°	60 "
IV	37.7°	34.6°	3.1°	35 "
V	37.6°	35.2°	2.4°	45 "
VI	37.1°	34.3°	2.8°	50 "
VII	37.5°	35.7°	1.8°	30 "
VIII	36.8°	35.7°	1.1°	50 "
IX	36.5°	35°	1.5°	40 "

X	37.2°	35.4°	1.8°	60	,,
XI	37.15°	35.6°	1.55°	60	,,
XII	37.2°	35.7°	1.5°	45	,,
XIII	37.4°	36.1°	1.3°	45	,,
XIV	37.6°	35.8°	1.8°	40	,,
XV	37.3°	35.5°	1.8°	30	,,
XVI	37.7°	36.5°	1.2°	45	,,
XVII	37.3°	35.6°	1.7°	60	,,
XVIII	37.8°	36.3°	1.5°	45	,,

As will be noted, the temperature differences on entrance were 3° and above, this difference decreasing steadily as the heart recovered strength.

CONCLUSIONS.

(1) The variation in temperature between rectum and hand in healthy persons averages 0.6° to 1.3° C.

(2) The variation in cases of cardiac disease is greater, except in aortic insufficiency.

(3) There is a characteristic difference in the peripherial circulation in aortic insufficiency as contrasted with other heart lesions.

(4) Muscular exertion, even to fatigue, in a person with a normal heart causes a rise in temperature in the extremities.

(5) Fatigue in a case of cardiac decompensation causes a fall in the peripheral temperature.

(6) Therefore, this method of temperature measurement is a simple and useful addition to the other methods in use for the examination of cardiac cases, and for the differentiation of cardiac sufficiency or insufficiency.

(7) It is a means of determining the effect of exercise, either active or passive, upon cardiac cases.

(8) It furnishes us with a method of distinguishing the edema arising from passive congestion from that due to nephritis.

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ON THE TRANSLATION OF CLINICAL DESCRIPTIVE TERMS INTO THEIR HISTOLOGICAL EQUIVALENTS IN DISEASES OF THE NOSE AND THROAT.

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THE mucous membrane of the upper air passages offers peculiar advantages for study, since within certain limits clinical deviations from the normal may be brought into direct correspondence with their histological phenomena. It is advantageous for the student to learn to associate the macroscopic with the microscopic appearances, as this practice not only gives added interest to his examination, but is of very direct value in the recognition and interpretation of the slighter departures from the normal.

The object of the following paper is to present a working scheme for the student, by aid of which he will be enabled to carry more readily in his mind this translation of terms. In such a scheme it would be found advantageous to omit consideration of new growths, since for obvious reasons, where such alterations are present, the most direct method is to excise a portion of the tissue, and examine it histologically. Such conditions as tuberculosis and syphilis are also omitted.

In the larger proportion, however, of diseases of the upper air passages, recourse to microscopic examination is not justifiable. If the student has clearly fixed in his mind the definite relation of clinical deviations from the normal with the histological changes, he will be enabled, on inspection, to approximate within narrow limits the more direct results of histological study. Inasmuch as the majority of the alterations which come under the observation of the laryngologist are superficial and displayed in the mucous membrane, a direct translation of clinical into histological terms would appear frequently possible. Where the alterations are more deeply seated, such a translation may be obtainable chiefly by inference.

The practical application of his method demands a clear knowledge of normal histology. The student should have readily available in his mind the salient features of the normal structure which he is inspecting. With this requirement presupposed, we may proceed to consider the scheme for study which it is proposed to offer. For convenience, we shall make the following division of the subject:

1. The visual details of the nose and throat.
2. The deeper structures invisible to the eye by reflected light.

1. The visual image of a given surface in the nose and throat is formed by the association of the structural units of the part. With an opaque surface, the image will be flat and in one plane, or

it may possess relative depth, dependent upon the degree of penetration of light rays below the surface.

The elements of the visual image are color, including translucence, shape or physical character of the surface, and presence of extraneous material which may be fluid, cellular or amorphous solid.

The color depends both upon the number, size and degree of distention of the blood vessels, and upon the ratio existing between the interstitial fluid and component cells. The translucence of the part depends upon the structure of the epithelium, and upon the amount of interstitial fluid near the surface. The shape or physical character of the surface depends upon the type and condition of the epithelial structures.

2. The deeper structures, invisible to the eye by reflected light, manifest their alterations by changes in shape, size and consistence. The shape depends upon the disposition of the subepithelial elements. The size is determined by the quantity of the various component units of the structure, both fluid and cellular. Consistence, recognized by probing, varies both in proportion to the quantitative ratio existing between the fluid and cellular elements, and according to the relative disposition of these to each other. The association of these different units in a definite fashion gives rise to the normal clinical picture, and by their variation are produced the various pathological alterations.

For purposes of space we shall restrict our examination in the present paper to the nose and faucial region.

THE NOSE.

Let us now take up some of the more common alterations of the nose and endeavor to interpret them histologically. We will consider, first, the normal histology of the tissue in question. Taking, for example, a section of the nasal tissues and examining it under the microscope, we find columnar ciliated epithelium, covering a thin mucous layer perforated by canaliculi through which there is a continual exosmosis of serous fluid to the surface. Below the mucous layer is a fibrous tissue of a varying degree of vascularity, containing mucous and serous glands, discharging their contents upon the epithelial surface. Between the fibrous tissue elements of this region is fluid in varying quantity, together with free cells, aggregated chiefly about the glands, and immediately below the mucous layer where it is disposed to form the lymphoid layer. We see thus that the normal appearances depend upon the association of a certain type of epithelium and of the mucous layer, upon the size, number and degree of distention of the blood vessels, upon the amount of interstitial fluid, the number and character of adventitious cells, and upon the character, degree of activity and number of the glands. Extraneous material is fluid and perceptible only as it lends a moist appearance to the surface.

Passing now to pathological alterations of the visible tissues within the nose, we may proceed to enumerate the various factors in the order already given.

Color may be increased diffusely or locally. If diffusely, and associated with increase in size, we may infer distention of the blood vessels; if with diminution in size we may believe that less interstitial fluid is present or fewer cellular elements, the blood vessels, therefore, relatively preponderating. The first condition is found in acute rhinitis, the second in atrophic rhinitis. Local heightening of color would denote the existence of circumscribed irritation as from previous trauma.

Diminution of color may occur from general anemia, or as the result of contraction of the blood vessels or from a relative increase in the other tissue elements. In pallor from anemia we find normal translucence, indicating that there has has been no change in the tissue cells or in the amount of interstitial fluid. If the blood vessels are contracted, symmetrical diminution in size is found, as after the application of cocaine or adrenalin. In pallor, without changes in translucence, and with increased size, we should expect increase either in the amount of the interstitial tissue or in the number of the glands or of the cells of the lymphoid layer. The character and amount of the surface fluid will here throw light upon the condition of the glands. In adults with increased resistance to the probe, fibrous tissue hy-

perplasia is probable, while in children with normal consistence of the part, we should expect increased infiltration in the lymphoid layer below the mucosa. In pallor with heightened translucence, we infer increase in the amount of interstitial fluid. If the amount of surface fluid is little or not at all increased, true edema is present without heightened exosmosis or glandular activity, as in nasal polypi. If the surface fluid is increased in quantity and thin or fails to coagulate on heating or treating with acid, we may infer widening of the canaliculi in the basement membrane and an increase in the interstitial fluid, as is found in vasomotor rhinitis. Such conditions may be either diffuse or local, and in the latter case their recognition may often be the chief clew to a correct diagnosis.

Loss of translucence of the epithelium, denoting disappearance of the columnar epithelium, occurs in various forms of atrophy, such as simple localized atrophy of the septal mucous membrane, in diffuse atrophy of ozena, and that occurring as the final result of syphilitic infiltrations. This loss of translucence is a factor of great importance in differentiating the atrophy of ozena from undeveloped turbinates, such as occurs in young women with associated arterial and uterine hypoplasia. In the latter case, the undeveloped turbinates give rise to the impression of atrophy, but inspection of their still translucent surface demonstrates the preservation of the columnar ciliated epithelium and excludes ozena.

By shape is denoted not only contour of the part as a whole, but also the texture of the surface. The contour may be changed as the result of irregular vascular dilatation, as in trauma or beginning abscess-formation, and is naturally associated with localized cellular infiltration. In the absence of hyperemia, it is found in localized hypertrophy of the various tissue elements, both in the mucous membrane and below as in the forms of hypertrophic rhinitis. Consideration of the factors of color, translucence, consistence and surface fluid will lead to a recognition of the special changes involved.

The texture of the surface depends upon the character and state of the epithelium.

Simple exfoliation of the epithelium may occur upon the mucous membrane of the septum as the result of trauma, but is practically not found in other regions. It may occur in association with increased vascularity as the result of a general inflammation characterized by desquamation. Such a condition is found particularly in the acute infectious diseases of the nose, and is recognizable by acute reddening and swelling of the mucous membrane with loss of translucence.

If the exfoliation of the columnar epithelium is of long duration or as the result of certain traumata, regeneration may occur by squamous epithelium. Under these circumstances certain clinical pictures are produced. In the first place, the loss of the cilia and the diminution in the number of the canaliculi, through which exosmosis

takes place, leads to the adhesion of mucus upon the spot involved. The loss of the motile cilia results in the failure of mucus to be transferred to other regions, and diminution in the normal quantity of fluid transuded to the surface permits the mucus to dry upon the parts. This alteration is found pre-eminently upon the septal mucous membrane and is also the direct result of extensive cauterizations or operations within the nose. The adhesion of tough mucus to a given region should lead immediately to the supposition that cilia and canaliculi have been destroyed.

Extraneous material upon the surface of the nasal tissues may be composed of nasal fluid or of cellular elements or of solidified material.

The nasal fluid is derived from several sources; first, from the mucous glands; secondly, from the columnar epithelium, which has undergone mucous degeneration; third, from the serous glands; fourth, from the canaliculi of the mucous membrane; fifth, from leucocytes which have escaped from the blood vessels to the surface; sixth, from condensation during expiration of aqueous vapor, exhaled from the lower air passages; seventh, from the lachrymal

This replacement of water is known to pass through the canaliculi of the mucous membrane. If these are contracted or obliterated, as in atrophic rhinitis, crusts form, while if a marked increase in transudation occurs as in vasomotor rhinitis, corresponding dilatation of these canaliculi is observed. In simple, chronic rhinitis, characterized by intermittent congestion and increased mucous secretion, there is a heightened proliferation, and mucous degeneration of the cells of the epithelium and of the mucous glands. In chronic hypertrophic rhinitis, and its various forms, papillary hypertrophy, edematous hypertrophy, there is an increase in the activity of the glands or the number of the canaliculi, but not proportionate to the increase in tissue.

In atrophic rhinitis, the glands are somewhat diminished in number and size, but the most striking alteration is the compact pavement epithelium and the absence of canals. In vasomotor rhinitis, we find an increase in the number and size of the canaliculi in proportion to the severity of the symptoms. The serous glands show, possibly, a heightened secretion, but the mucous glands show no evident increase in activity.

Bearing these facts in mind, we may now ask ourselves, in the examination of a given case, characterized by abnormal nasal secretion, does the condition represent excessive or diminished activity on the part of the mucous glands, or is there mucous degeneration in the surface epithelium, or transformation of the latter into squa-

mous cells? Is there abnormal patency or contraction or obliteration of the canaliculi; is there increased migration of leucocytes to the surface or abnormal condensation of moisture exhaled from the lower air passages? These questions must be supplemented by an inquiry into the remaining elements of the clinical picture, and the answer will be forthcoming by a consideration in the manner above described of all the factors involved. Other extraneous material upon the surface as blood or fibrinous exudate needs only passing mention.

THE FAUCES.

We may proceed in a similar way to examine the faucial region. For brevity, the posterior pharyngeal wall and tonsils will be alone considered.

On the posterior pharyngeal wall, we find histologically epithelium of the pavement type, overlying a stout, compact mucous layer, which is united by layers of fibrous and yellow elastic tissue to the muscular bands below. Imbedded immediately below the mucous membrane are aggregations of lymphoid cells of varying size and number, the follicles of early life, which pass, with increase in age, into masses of vascular and fibrous tissue, and covered by thinner mucous membrane, the so-called granules of the pharynx.

In the tonsil the unit of structure is the follicle, a collection of lymphoid cells inclosing a central endothelial reticulum. These units are sepa-

rated from each other by an endothelial network containing lymphoid cells, plasma cells, and cells of a type intermediate between these two. The surface of this tissue is formed by mucous membrane, squamous or columnar, of considerable density, equaling, at least in compactness, the mucous membrane of the vicinity. The stout mucous membrane of the free surface forms invaginations, which are lined with comparatively loose mucous membrane.

Increased reddening of the parts may be the result of acute hyperemia or passive congestion. In the former instance, if there is associated swelling, we shall expect histologically either increase of interstitial fluid or cellular infiltration, the two conditions being differentiated by the relative translucence or opacity of the enlargement. In the passive congestion of chronic inflammation or of systemic disease, there is symmetrical thickening with diminished or unaltered translucence. While it may be difficult on the posterior pharyngeal wall to recognize thickening of the mucous membrane, we may often infer its existence from an examination of the uvula, at the tip of which it can be more readily perceived.

Pallor of the pharynx and tonsils denotes usually general anemia, as we do not find here the various other causes which are present in the nose.

Changes in shape and size may be advantageously considered together. On the posterior pharyngeal wall, the mucous membrane may be

thickened, with or without associated enlargement of the follicles or granules. In this case there is generally concomitant reddening as already described, denoting chronic inflammation. Enlargement of the follicles alone is the common change found in early life and indicates simply proliferation of the lymphoid elements. Enlargement of the granules is usually associated with reddening, and evidence of fibrous tissue hyperplasia in the vicinity.

In the tonsils, increased size may or may not be symmetrical. With unchanged color a symmetrical increase denotes proliferation of all the tissue elements in essentially normal proportion. Irregularity of the surface in the form of mamillations or digitations, particularly about the lacunæ, especially if associated with heightened translucence, may denote rapid proliferation of the lymphoid elements out of proportion to the relatively slower rate of increase in the fibrous tissue.

Diminution in the size of the tonsils suggests naturally the disappearance of a definite number of the lymphoid elements, with preservation of the fibrous tissue, the organ becoming simultaneously more opaque and dense.

In the faucial region, consistence is relatively seldom a diagnostic factor, but in localized swellings may help to differentiate between an abscess and a new growth.

Extraneous material in this region demands only brief consideration. Except for the presence of detritus in the lacunæ of the tonsils, and of

fibrinous exudate upon the mucous membrane, the material found here is fluid and has come from other regions.

A test of the above necessarily incomplete suggestions for clinical examination will show in practice many directions in which additions and expansions can be made. The writer has found the plan of distinct service in his teaching, and is encouraged to offer it for the consideration of other instructors. While it may not be necessary for the student to consult or follow absolutely this plan in the examination of a given case, yet it is believed that approximate adherence to it will prove of distinct value, both in encouraging a more painstaking clinical examination, and in facilitating the deductions to be drawn from his inspection.

THE CLINICAL VALUE OF THE ESTIMATION OF AMMONIA IN DIABETES.

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THE large quantity of ammonia in the urine of diabetic patients has attracted attention since Hallerworden first discovered its presence in 1880, but its value in the clinical estimation of the degree of acidosis has not been generally appreciated. Various observers working especially along diabetic lines emphasized its importance, yet the test has not been widely adopted by the profession. This has been due in part to the length of time consumed in the performance of the test by the Schlösing method, and in part to the attempt to judge of the degree of acid poisoning by other methods, such as the estimation of acetone and diacetic acid or B-oxybutyric acid. Folin's recently devised method [1] for the determination of

* Aided by the Proctor Fund for the Care and Study of Patients with Chronic Disease. The cases upon which this article was based occurred in the practice of E. P. Joslin. A portion of the chemical work was done by Elsie H. Newman and E. P. Joslin, but by far the greater part of the analyses were made by H. W. Goodall.

[1] Hoppe-Seyler's Zeitschr. für Phys. Chemie, Bd. 37, Heft 2, Nr. 11, 1902.

ammonia has shortened the time required for the test from three days to one to three hours, and has thus made it clinically practicable. On the other hand many investigators have shown how little reliance can be placed upon determinations of acetone and diacetic acid as expressions of the total acidosis; and finally a simple method for the determination of the chief acid factor, B-oxybutyric acid, still lacks a discoverer. Moreover, even if ready methods for the estimation of these three acid bodies were known, their employment would only show the total amount of these bodies removed from the organism; they would give no hint of the quantity of acid which was left behind. This objection does not hold against ammonia, because it registers the effort which the body is making to protect itself from acid poisoning. At the present time it appears safe to regard ammonia in this light, although it is not justifiable to use the ammonia as such a criterion in the last hours of life, when Nature loses, one by one, all her powers of self-preservation.

Ammonia may be a very good index of acid production in the body and perhaps is the most accurate method we have for this purpose, but it is not claimed that ammonia is the best or only good test of the severity of a case of diabetes. Pancreatic diabetes certainly runs its course without markedly influencing the ammonia production.[2] It is a question for further study as to whether the carbohydrate balance may not be

[2] Brügsch: Die Therapie der Gegenwart, Bd. xlvii, 337, 384, 1906.

just as good a guide for prognosis as the ammonia. It is indeed true that the determination of the severity of a case of diabetes by the estimation of ammonia is less subject to error than the determination of the carbohydrate balance, and for the following reasons. The quantity of ammonia excreted in twenty-four hours is an easily attainable fact like the total output of sugar, but the quantity of carbohydrates ingested by the patient during the same period lacks control. It is not possible to be sure of the extent of a positive or negative carbohydrate balance unless the patient is isolated. This is rarely practicable. One of our patients who contributed $100 to the Fund for Diabetic Research at the Harvard Medical School confessed that during the very period we were trying to influence his acidosis in a most painstaking and expensive experiment, he was surreptitiously eating freely of carbohydrates.

The normal quantity of ammonia excreted in health varies between 0.4 gm. and 1.5 gm. in twenty-four hours, and the per cent of nitrogen in the form of ammonia to the total nitrogen of the urine (ammonia-nitrogen ratio) varies in health between three and five per cent. It is directly dependent upon the quantity of nitrogenous food in the diet. Schittenhelm and Katzenstein[3] were able to show that these figures were practically constant, even though the quantity of nitrogenous food varied greatly. This fact is of importance, because otherwise it would be unjustifiable

[3] Zeitschr. für exp. Path. Therapie, Bd. 2, S. 542, 1906.

to conclude that an increase in the ammonia nitrogen ratio was an expression of increasing acidosis. Schittenhelm's work would appear to answer the objection raised by Fr. Müller[4] upon this point.

The quantity of ammonia in cases of diabetes mellitus is generally high on account of the excess of albuminous food which such patients consume when their choice of diet is left to themselves. Conclusions as to the value of reported quantities of ammonia in the urine should only be reached when this has been taken into account. Thus, an amount of ammonia is abnormal which reaches 1.5 to 2.0 gm. with a metabolism of 100 gm. albumin, and suggests acidosis, but it would be perfectly normal with a metabolism of 200 gm. albumin. Contrary to our preconceived ideas and to commonly accepted opinion, we found that although diabetic patients often take rather large quantities of albumin, they seldom eat excessive amounts. For example, of 13 patients only 8 excreted more than twenty grams of nitrogen (20 x 6.25 = 125 gm. albumin) in the urine in twenty-four hours, and only four patients more than twenty-five grams. The total number of analyses made was 146, but only fifteen times was Atwater's standard quantity of daily albumin (125 gm.) exceeded. When once the attention of a patient was directed to the importance of eating vegetables and fat, it was rare that the quantity of albumin in the diet reached as much as one hundred

[4] v. Leyden's Handbuch der Ernährungstherapie, 2 Aufl., S. 261, 1903.

and twenty-five grams. Mild cases of diabetes produce no more ammonia than ordinary individuals, but the advanced cases show amounts of ammonia and an ammonia-nitrogen ratio which are reached in no other condition.

Case No. 163, referred to us by Professor Mendel, is an illustration of a mild case of diabetes with normal ammonia. The patient, a woman, developed diabetes at the age of forty-five, August, 1905, and on Aug. 21, 1907, showed 5.8% sugar, 59 gm., in twenty-four hours. She became sugar-free eight days later, and by Jan. 16, 1908, had acquired a positive carbohydrate balance of 94 gm. On Oct. 10, 1907, the quantity of nitrogen in the urine was 19.3 gm. and the ammonia 1.2 gm., giving an ammonia-nitrogen ratio of 5%.

Examples of the excretion of large quantities of ammonia in severe cases of diabetes will later be mentioned.

If ammonia is to be used as an index of acidosis, it is, therefore, necessary to know the amount of albumin in the diet, as has been above mentioned. The quantity of albumin which the patient is eating can roughly be determined by estimating the nitrogen in the urine, but the ordinary tests for urea,[5] as a rule, in diabetic urines are inaccurate. On the other hand, if the patient is willing to weigh the food it is easy to calculate the quantity of albumin in the diet.[6] If great accu-

[5] Joslin: Jour. Med. Res., vol. vi, p. 319, 1901.
[6] Joslin and Goodall: A Diabetic Chart. Boston Med. and Surg. Jour., vol. clviii, p. 248, 1908.

racy is desired it would, of course, be necessary to prescribe the special form of albumin, because considerable and varying quantities of carbohydrates may be formed in the body from albumin, and the oxidation of carbohydrates influences the acidosis and thus the ammonia. In clinical work this is not necessary, and one will not go far wrong if a diet containing 100 gm. albumin is prescribed of which 75 gm. are to be taken in the form of meat or fish (300 gm.) and the remaining 25 gm. left to the choice of the patient.

A knowledge of the approximate quantity of carbohydrates in the diet is essential, or at least of advantage, in the interpretation of the ammonia, because even a normal individual without carbohydrates develops acidosis, and the diabetic does this even to a greater degree. On the other hand, diabetic patients of known severity may at times excrete enormous quantities of carbohydrate, and yet have little ammonia in the urine. This is explained by the fact that all diabetics, no matter their severity, are capable of assimilating some of the carbohydrates ingested. Great quantities of carbohydrate may thus temporarily mask an acidosis. For these two reasons, therefore, it would be helpful if the test for ammonia was made when the patient took a standard quantity of carbohydrate, but just what this quantity should be, it is not such an easy matter to decide. One would not wish to give a patient, who has become sugar-free only after laborious and painstaking treatment, a quantity of carbohydrates in excess of

what he can assimilate. A break in his upward course would be established from which it would take much time to recover; on the other hand, it is equally poor dietetic management of a case of diabetes to suddenly restrict the carbohydrates to a low level. In this dilemma one naturally turns to the carbohydrate balance, but its capability for error has been pointed out. It would be interesting to know whether with the same negative and positive carbohydrate balance different patients on similar diets excreted the same amount of ammonia. On this question we have not as yet sufficient data. So far as we are able to judge most of our patients were using fifty to one hundred grams carbohydrate daily, and it is most probable that all those about to be reported had a minus carbohydrate balance.

The administration of an alkali to a diabetic patient with acidosis directly affects the ammonia in the urine. Theoretically, 1 gm. of ammonia manufactured by the patient is equivalent in neutralizing power to 5 gm. sodium bicarbonate, but practically much more extraneous alkali is necessary. Thus, v. Noorden found that in 10 cases, where the ammonia excreted was 4 to 6 gm. the taking of 30 gm. sodium bicarbonate daily was followed by a diminution of only ten to twenty-two per cent in the ammonia.[7] We can record a similar instance. Case No. 135 excreted 5.1, 5.2, 5.3, and 5.0 gm. ammonia on four successive days without taking alkali; on the following

[7] v. Noorden: Handbuch der Path. d. Stoffwechsel, Bd. II, S. 83, 1907.

two days 25 gm. sodium bicarbonate were given and the ammonia changed to 4.2 and 5.2 gm.; on the next two days 37 gm. sodium bicarbonate were daily administered and 15 gm. additional were introduced by enema on the second day, yet the ammonia was 5.2 and 4.7 gm. respectively. It is only fair to say that upon these last two days the diet was not quite constant and coma was approaching. It is, therefore, best to estimate the ammonia when alkali has not been used for some days, but, at any rate, if an alkali is coincidentally given this amount should be stated. The error introduced by alkali, however, is seldom over twenty per cent.

During the last year and a half we have studied the quantity of ammonia excreted in the urines of most of the severe cases of diabetes which have come under our observation. They all represent advanced types of the disease; and except in one or two instances, which are cited for special reasons, they had a considerable minus carbohydrate balance. Most of these patients have already died. The cases fall naturally into two groups and can best be classified according to age. We will first report seven cases occurring in patients under forty years of age and, later, six cases between the ages of fifty and sixty years.

The first case will be reported in detail, because the patient was under observation for several weeks at the House of the Good Samaritan and the diet was under control.

No. 94, a dressmaker, unmarried, who had lost a sis-

ter of diabetes in diabetic coma and one brother and two sisters of tuberculosis, developed symptoms of diabetes during the summer of 1902, at the age of thirty-nine years. She came under our observation in July, 1905. Weight, 116 lb.; previous best weight 150 lb., weight in 1904, 145 lb. Urine, 3,580 ccm., 279 gm. sugar, diacetic acid + +.‡ Under treatment the sugar fell in August, 1905, to a minimum of 21 gm. and the weight rose to 121 lb. In the autumn the sugar was 100 gm., and remained at about that level until a year later, Nov. 7, 1906, when the patient entered the House of the Good Samaritan. Her weight was then 118 lb. While at the hospital her diet was modified in many ways as shown by Chart I, (page 648), in order to determine the character of the carbohydrate which she would bear best. Twelve grams of sodium bicarbonate were taken daily throughout the stay in the hospital.

The quantity of carbohydrates in the diet between Nov. 7, 1907, and Dec. 15, varied only between 55 gm. (Period V) and 80 gm. (Period II), although there was much alteration in the sort of carbohydrate administered. The assimilation of carbohydrate generally improved with the stay of the patient in the hospital and was best in the period in which oatmeal formed the chief proportion of carbohydrate (Period VII), perhaps due to the slow excretion of carbohydrate in oatmeal,[8] and when the total carbohydrate administered was lowest (Period VIII). This is proven by a comparison of the carbohydrate balance. This was minus throughout the stay in the hospital and well exemplifies the severity of

‡ It is our custom to record the result of Gerhardt's ferric Chloride test for diacetic acid with one to four + signs, according to the strength of the reaction.

[8] Falta and Gigon: Zent. für ges. Phys. u. Path. des Stoff. N. F. ii., s. 241, 1907.

the disease in this patient. There were two exceptions to this rule: the first, the last day of the oatmeal period, Dec. 8, when the balance was zero. Investigation showed that this figure represented a false showing as the patient became so nauseated by the oatmeal that she vomited some of it — a not exceptional occurrence if such a diet is given. The carbohydrate balance was positive on Nov. 15. Evidently, an error occurred in the collection of urine or in the record of urine, or the patient did not eat all allowed carbohydrates, for it is impossible to believe that a minus carbohydrate balance would change to a positive balance on one day alone in a series of thirty-eight days. This illustrates the advantage of recording a carbohydrate balance if one wishes to know what is actually taking place in a case of diabetes.

The carbohydrate balance of minus one hundred and thirty grams on Nov. 7, the first day after entrance, is obviously wrong. This is easily shown because the total nitrogen for the day was but 13.3 gm. (13.3 x 6.25 =83 gm. albumin), and from this quantity only 50 gm. carbohydrate (83 x 60% = 50 gm. amount carbohydrates formed out of albumin in the diet) could be formed. This is easily explained. The patient's diet before entrance to the hospital was undoubtedly much more liberal in carbohydrate. The following four days showed a steady drop in the sugar of the urine, although the carbohydrates in the diet remained the same. This is a common occurrence when diabetic patients are placed on a measured diet.

The absolute amount of ammonia which was excreted varied but little with the various changes in diet made. No constant relation can be noticed between it and the carbohydrates in the diet or urine or the carbohydrate balance, because the ammonia was

both at its lowest (Period II) and highest (Period VII) levels when the carbohydrate balance was low. In other words, variations amounting to 25 gm. of carbohydrate in the diet of a severe case of diabetes with a minus carbohydrate balance of 20 to 40 gm. show no effect on the acidosis as measured in terms of ammonia. Further, it would appear that the restrictions of diet to 100 gm. carbohydrate, when a patient has been taking double that amount, is a perfectly safe procedure. The constancy of the amount of ammonia excreted on successive days is reassuring. This is notable in Period I and Period II, also in periods III, IV, V, VI, and again in periods VIII and IX. The large amount of ammonia in the oatmeal Period VIII is not what we should have expected.

The closeness with which the ammonia-nitrogen ratio follows the total ammonia is at once striking. On Nov. 9, the total ammonia was 4.8 gm., one of the highest limits reached in this case. Without a knowledge of the total nitrogen on that date, an erroneous impression of the severity of the case would have been gained. The great increase of total nitrogen, however, accounts for it, as the change in the ammonia is but little greater than would be expected with the increase of nitrogen. The ammonia-nitrogen ratio in this instance is probably a safer guide to the true acidosis than is the total ammonia. This would also seem apparent by a comparison of the total ammonia and the per cent of nitrogen in the form of ammonia on the following days:

Date.	Total ammonia grams.	Ammonia-nitrogen ratio.	Total nitrogen gram.
Nov. 9	4.8	26%	15.5
Dec. 5	5.2	37%	11.7
,, 7	4.7	34%	11.4
,, 8	4.6	39%	9.8

The quantity of ammonia remains practically constant on these four days. Without a knowledge of the total nitrogen and by its means the determination of the ammonia-nitrogen ratio the change in degree of acidosis on Dec. 5, 7, and 8, as compared with Nov. 9, would be entirely overlooked, but the change in the ratio makes it apparent.

The patient gradually failed after discharge from the hospital and died March 24, 1907. It is noteworthy that the ammonia reached its maximum, 5.2 gm. (nitrogen 11.7g m., ammonia-nitrogen ratio 37%), on March 23, 1907, the day preceding coma, but that on the day of coma the ammonia-nitrogen ratio and the total ammonia were not particularly great. Two factors may account for this circumstance, — the small quantity of urine voided and the failure of the organism to react to the demand for alkali. The former explanation would appear to be more correct, if one compares other cases of coma in which the ammonia-nitrogen ratio constantly rose as coma advanced, despite the administration of enormous doses of sodium bicarbonate.

A similar case (No. 139) is that of a girl, a patient of Dr. H. O. Smith, Hudson, N. H., who first noticed polyuria in February, 1906, at the age of nineteen, and came under my observation in October, 1906. The course of the disease is shown by the accompanying Chart II.

This patient also received 12 gm. sodium bicarbonate Oct. 30, 1906, until death, Dec. 23, 1907. The progressive character of the acidosis is significant. The first obvious change in the ammonia was the well-known increase following the preliminary restriction of carbohydrates. In consequence, the total ammonia rose from 4.2 gm. to an average of 5.5 to 6.1 gm. during the following two months in which the carbohydrates were lowered from approximately two hun

dred grams to one hundred grams in twenty-four hours. In cases of diabetes which are not of unusual severity this preliminary increase in ammonia may pass away with improvement in the general condition. Its persistence is of ominous significance.[9] There is no doubt about the increase of ammonia representing a real acidosis, because the total nitrogen was reduced nearly one half during these two months. This is strikingly evident if one compasses the figures for Oct. 30 and Dec. 23. The total nitrogen on the latter day is one half of the former, but the ammonia increased 40%. The per cent of ammonia in this instance is certainly a more valuable index of the total acidosis than the total quantity of ammonia. The well-being of the patient up to the very onset of coma was striking, and in conformity with clinical experience. On Nov. 29 the ammonia excretion reached 7.3 gm., the highest amount which we have noted in any of our patients. It is most unfortunate that the total nitrogen was not done on this day. The appearance of the patient in no wise indicated the gravity of the disease, but the high amount of ammonia showed the rapidly approaching fatal acid poisoning and allowed an accurate prognosis. Yet it is noteworthy that the ammonia amounted to 6 gm. even one year before. The extent of the minus carbohydrate balance well illustrates the intensity which the disease had reached.

Case No. 135 is that of a man who developed the first obvious symptoms of diabetes in the spring of 1903, at the age of twenty-nine. The total quantity of urine at that time was seven qts. and the amount of sugar excreted about one pound a day. He was referred to me by Dr. George C. Shattuck, in September, 1906. In the spring of 1907 he entered the New England Deacon-

[9] v. Noorden: Handbuch der Path. d. Stoffwechsel, Bd. ii, S. 55, 1907.

ASE No. 139.

6, 123¾; Dec. 16, 1907, 120½.

ent f gen.	Urine, total sugar.	Total carb.	$NaHCO_3$.	Carbohydrate balance.
	gm.	gm.	gm.	gm.
5	198		12	
3	176		12	
3	129	70	12	—50
6			12	
6	109	63	12	—45
1	96		12	
1	95		12	
1	68		12	
1			12	
0	86		12	
0	97		12	
	138		12	
	86		12	
	108	44	12	—65
	120	62	12	—60
	128	68	12	—60
	90	50	12	—40
death				

ASE No. 135.

Ammonia.		Urine, total sugar.	Total carbohydrates.	$NaHCO_3$	Weight of patient.
Total.	Per cent of nitrogen.				
gm.		gm.	gm.	gm.	lb.
		490			
		188			127½
3.2	11	173		20	128½
2.7	11			16	130½
3.2	12			12	132½
6.8		192		12	
6.1		171		12	
6.9		246		12	
6.1		212		12	
		386			121
		288			
5.1	19		135	0	88½
5.2	22		135	0	89½
5.3	21		135	0	86½
5.0	21		135	0	85½
4.2	21		135	25	85
5.2	23		120	25	83½
4.0	18		130	37	82½
4.2	21		70	52	81½
3.0	17		15		
eath in coma.					

Date.	Order by note below	Gm.
1906		
Oct. 30		
Nov. 14		—50
Dec. 5		
" 6		—45
" 9		
" 11		
" 14		
" 18		
" 21		
" 23		
" 24		
1907		
Jan. 19		
April 21		—65
Aug. 13		—60
Oct. 21		—60
Nov. 29		—40
Dec. 16		
" 23		

Date.	$KClO_3$	Weight of patient.
1903		
Sept.		lbs.
1906		
Sept. 27		
Oct. 11	20	127½
Nov. 6	16	128½
Dec. 4	12	130½
1907		132½
March 12	12	
" 13	12	
" 14	12	
" 15	12	
May 10		121
July 5		
Nov. 27		
1908		
Jan. 20	0	88½
" 27	0	89½
" 28	0	89½
" 29	0	89½
" 30	25	85
" 31	25	83½
Feb. 1	25	82½
" 2	25	82½
" 3	25	81½
" 4		

ess Hospital for two weeks, where he regained some of his strength. The previous summer and the following summer he improved much while at the Massachusetts General Hospital. Finally, in a most exhausted condition, in January, 1908, he again entered the New England Deaconess Hospital, having lost 50 lb., and after nine days died of coma.

The increase in ammonia from the fall of 1906 to the spring of 1907 was striking and showed the severity of the disease still more than did the loss of weight. In these latter months the diet was certainly far less restricted than before, but an accurate idea of it cannot be formed because the patient was outside of the hospital. Despite the high amount of ammonia, however, the patient, like the previous one, was able to work for the greater part of the time while under observation. In January, 1908, he was in a pitiable condition, voiding large quantities of urine. He had given up on his own account the sodium bicarbonate which he had taken intermittently for nearly two years. His weight was 88 lb. For the four days, Jan. 26 to 29, inclusive, he continued without soda on a diet consisting of 110 gm. albumin, 185 gm. fat and 135 gm. carbohydrates. He was then given 25 gm. of sodium bicarbonate daily. The diet remained unchanged, but two days later distinct drowsiness appeared, accompanied by increasing weakness, and on Feb. 2 coma developed. The average amount of ammonia excreted during the first four days was 5.2 gm., and for the last four days 4.5 gm., despite the fact that considerable quantities of sodium bicarbonate were given in this period. Presumably the acidosis greatly increased during that time, but the ammonia unfortunately gave no signal of increasing danger during the period the patient was in the hospital.

Case No. 4 is of interest in this connection because the patient was under close observation during coma. A boy, fifteen years of age, developed symptoms of diabetes in 1897. In August, 1898, he consulted Dr. J. J. Putnam, who kindly transferred the case to me. The course of the disease is shown by Chart IV.

It will be seen that the ammonia rose as coma progressed, despite enormous doses of sodium bicarbonate. The ammonia-nitrogen ratio rose even more steadily than the total quantity.

Case No. 74 also illustrates the progressive upward trend of the ammonia in severe diabetes. A boy of fifteen developed symptoms of diabetes in January, 1904; a month later sugar was found in the urine, and treatment was begun by Dr. F. H. Thompson, of Fitchburg, for whom I occasionally saw the patient. The boy remained in comparatively good health up to a very short time before his death in December, 1907, just one month lacking four years of proven diabetes. No other case of a child living so long has come under our care. It would interest us much to learn of other such cases. This patient does not show a progressive acidosis so well. It may well be that some error existed in the diet or in the collection of the urine. At any rate these are the uncertain data with which one is often compelled to work in private practice. It must be conceded that the ammonia failed to adequately warn of imminent danger. It was higher eight months than one month before death. The course of the disease is shown by Chart V.

Case No. 162 was that of a man who developed diabetes in the spring of 1904, at the age of twenty-seven years. Sugar was not found until October, 1905. He first came under our observation in May, 1907, when the urine showed 5.7 gm. of ammonia in twenty-four

V. Case No. 4.

A. of ro-n.	Urine, total sugar.	$NaHCO_3$.	Weight of Patient	Remarks.
	gm.	gm.	lb	
	520	10–20		
	76	10–20	92	
	312	10–20	100	
	170	10–20		
	165	10–20	108	
	144	10–20		
	357	10–20	105	
.4	276±			Coma began during last six hours.
1	167	113		Coma relieved 2 hours after onset.
:0	233	140		Coma relieved.
:5	61	92		Coma returns.
	10	6		Coma deepens; death.

V. Case No. 74.

Ammonia. Total, grams.	Ammonia. Per cent of nitrogen.	Urine, total sugar, grams.	$NaHCO_3$, grams.	Carbohydrate, balance.	Weight of patient, pounds.
		30			92
		0			
		21			
		69			
		107			
3.2	22	77	8		
3.5		65	8		106
5.8		103	8		104
4.0		98	12	—32	

:oma, Dec. 16, 1907.

hours. He barely held his own during the summer and died in November, 1907. The large amount of ammonia was suggestive at the start, but not more suggestive of impending trouble than the appearance of the patient. It is instructive to compare this case with the former one just reported as an example of the advantage of careful treatment. In the former instance, a boy of fourteen years came under the care of Dr. Thompson soon after the appearance of the disease, and lived approximately four years; in the latter, a man of twenty-seven years did not begin treatment until eighteen months elapsed from the onset of the disease, and lived but three and a half years. Treatment in the case of the boy more than counterbalanced the advantage that usually goes with advancing age in diabetes. The following chart shows the course of the disease:

CHART VI. CASE No. 162.

Best weight, 154.

Date	Vol.	Total Ammonia	Urine, total sugar.	$NaHCO_3$	Weight of patient.
1907.	c. cm.	gm.	gm.	gm.	lb.
May 20,	6,000	5.7	345	12	114¼
Sept. 2,					119⅝
,, 27,	4,750		152	16	

Death in coma, Nov. 28, 1907.

Case No. 146 is another instance in which the ammonia suggested an early fatal issue. The patient was a colored railway porter who developed the first symptoms of diabetes at the age of twenty-nine, and was seen in consultation with Dr. Dewis a year and nine months later. His physical appearance did not warrant an immediately serious prognosis, but the urine showed 6.7 gm. ammonia. Death occurred in coma two months later. This quantity of ammonia has been exceeded only three times in our experience, namely, in cases No. 135 and No. 139, of whom the former died in

eleven months and the latter in one month after the observation was made, and in Case No. 147 who had 7.0 gm. ammonia on March 8, 1908, and is alive at the present time, April 20, 1908. This last patient had 3.0 gm. ammonia one year ago.

SEVERE DIABETES BETWEEN FIFTY AND SIXTY YEARS OF AGE INCLUSIVE.

The following six cases represent our second group. They have various points of similarity to one another and present a distinct contrast to the seven cases just reported. They all came under our observation between the ages of fifty and sixty years inclusive. All showed quantities of ammonia far less than those of the preceding group, and although there was a marked minus carbohydrate balance, it was of less extent. All died within a comparatively short time after a moderate acidosis developed. Until this point occurred they had lived in comparative comfort for many years. These cases will be briefly summarized, but the following table, Chart VIII, will show some of the facts. For contrast the two groups of cases are presented together.

Case No. 42, male, was referred to me by Dr. William Bolton, of Athol, in December, 1902. Sugar was first discovered in 1884 during an examination for life insurance, but it later disappeared. By 1892 it had returned in sufficient amount to demand active treatment. The past history was negative except for an attack of rheumatic fever. Arteriosclerosis was noted at my first examination. Four years later an attack of hemiplegia occurred, and death followed six months

146.

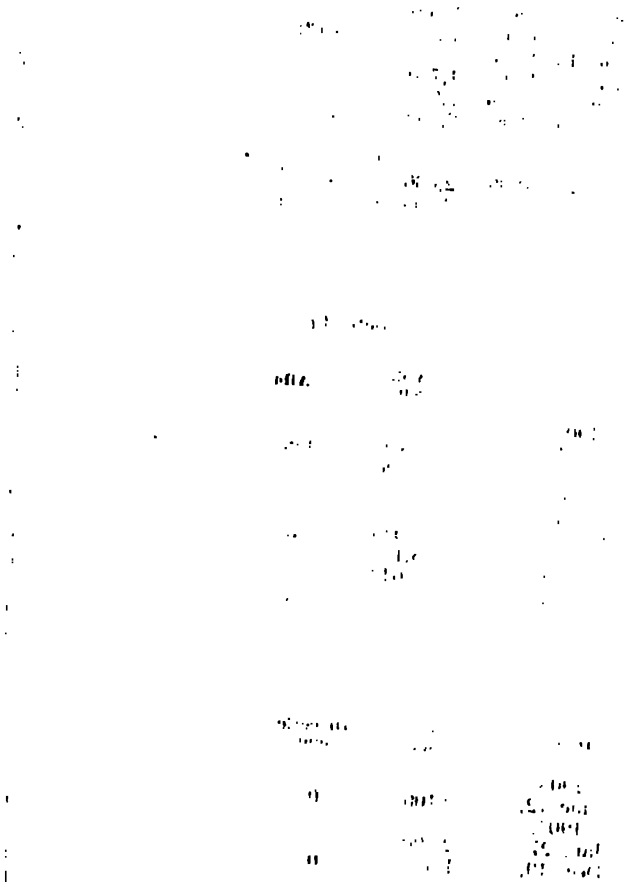
901.

AMMONIA. Per cent of nitrogen.	Urine, total sugar, grams	Weight of patient, pounds.
19.0	274	118

07.

of age

Urine total sugar, grams.	Date of fatal coma.	Duration of disease.
84	March, 1907,	5 years
128	December, 1907,	2 ,,
192	February, 1908,	5 ,,
233	October, 1900,	3⅛ ,,
103	December, 1907,	3¼ ,,
345	November, 1907,	3½ ,,
274	February, 1907.	1½ ,,
ears of age, inclusive.		
80	July, 1907,	23 ,,
80	February, 1907,	3½ ,,
70	August, 1906,	3½ ,,
77	July, 1907	2¼ ,,
79	September, 1907,	2½ ,,
124	December, 1907,	3½ ,,



later, July, 1907, in coma. The course of the disease is shown by Chart IX.

Case No. 101, male, was referred to me by Dr. George G. Sears. He was later under the care of Dr. Thomas Walker, in St. John, N. B. Diabetes was discovered in September, 1903, at the age of fifty-five years, at which time 175 gm. of sugar were excreted in twenty-four hours. Arteriosclerosis was noted on the date of the first examination, Nov. 19, 1905. The gain in weight in December, 1906, was probably in great part due to dropsy and in another paper we expect to report observations on this subject. The course of the disease is shown by Chart X.

Case No. 108, male, was referred to me by Prof. R. H. Chittenden, December, 1905. Diabetes was first discovered in March, 1903, when the patient was forty-seven years of age. No arteriosclerosis was noted. Albumin was absent from the urine December, 1905, but a slight trace with numerous casts appeared in April and persisted until the death of the patient in August, 1906. The patient appeared in good condition even up to the day preceding coma. Chart XI.

Case No. 138, sister of No. 101, came under my observation in October, 1906, having had diabetes since the spring of 1905, when she was fifty-eight years of age. Arteriosclerosis was not present, but the urine showed hyaline and fine granular casts. The course of the disease is shown by Chart XII on the following page.

Case No. 145, male, was referred to me by Dr. Mortimer Warren, of New York City. Symptoms of diabetes were first noticed in February, 1905, at the age of fifty-three years. The patient came under my observation in December, 1906. Arteriosceleros was present, together with mitral insufficiency of moderate degree. The course of the case is shown by Chart

XIII for a portion of which we are indebted to Dr. Warren.

Case No. 137, male, was referred to me by Dr. C. A. Lovejoy and Dr. Sarah E. Palmer. He developed symptoms of diabetes in June, 1904, at the age of fifty-three, but at no period followed any physician's directions for more than a brief interval. Moderate arteriosclerosis was present, and there was a slight trace of albumin in the urine with a few hyaline casts. The patient first came under my observation in September, 1906. The ammonia-nitrogen ratio of 27% implied a much more serious prognosis than did the aspect of the patient, and he was consequently allowed to go to California. The trip was borne well and on his return in the spring he was able to resume work for some months. At length, in December, 1907, he died in coma. Chart XIV.

Diabetes occurring in the sixth decade is considered to be a comparatively mild disease and one is not warranted in attacking this conception because of the cases above reported. We could cite many patients now under our care whose appearance would not disclose impaired health. Most of these reported cases, although they began in mild form, presented a severe type of the disease when they came under our observation. In not one case was it possible to keep the urine free from sugar for more than twenty-four hours. Diacetic acid, therefore, was, of course, invariably present. The diet in all instances after a preliminary period of observation contained at least 50 gm. carbohydrate, and most of the patients took about 12 gm. sodium bicarbonate daily from the time

CASE No. 138.

ght, 145 lb.

n,	Ammonia. Total, grams.	Ammonia. Per cent of nitrogen.	Urine, total sugar, grams.	$NaHCO_3$, grams.	Weight of patient, pounds.
	1.0	5	22	4	
	1.7	9	29	4	
	1.5	5	39	4	
	0.8	5	48	4	
	3.4	17	43	4	124
		20			
	3.2		77	12	

na, July 12, 1907.

CASE No. 145.

, 1906, 138 lb., then rose to 152 lb.

Ammonia. Total, grams.	Ammonia. Per cent of nitrogen.	Urine, total sugar, grams.	$NaHCO_3$, grams.	Weight of patient, pounds.
		77		
	8	104		
	6	64		
	5	77		
	10	108		
		100	6	Dec. 15, 150
1.4	11	82	6	Dec. 23, 148
1.6	10	79	6	147
1.8	12	97	6	
4.0		99	12	
3.6		70	12	
4.1		104	12	145
3.6		101	12	
3.4		102	12	
1.7	14	55	12	
2.4	13	79	12	147

in coma, Sept. 2, 1907.

CASE No. 137.

Weight, Sept. 25, 1906, 121 lb.

Ammonia. Total, grams.	Ammonia. Per cent of nitrogen.	Urine, total sugar.	$NaHCO_3$, grams.	Weight of patient, pounds.
				Oct. 19, 121
		6% grams		
4.7	26	230	12	
5.8	27	124	12	122

ma, Dec. 23, 1907.

we first saw them until death. No notable loss of weight was experienced by any patient. The cases illustrate the seriousness of a moderate acidosis in old people in comparison to the severity of such a condition in young individuals.

CONCLUSIONS.

1. Quantities of ammonia reaching 5 gm. in twenty-four hours indicate an extremely severe form of diabetes, which usually proves fatal within a year.

2. Patients under forty years of age tolerate an acidosis estimated in terms of 4 to 5 gm. ammonia far better than those above fifty years tolerate an acidosis of 2.5 to 4 gm. ammonia. An acidosis in an individual above fifty years of age is of very serious prognostic import.

3. A knowledge of the ammonia excretion usually helps in the treatment of a case of diabetes, and generally, but not always, gives warning of impending danger.

4. The value of a knowledge of the ammonia excretion in the prognosis of a diabetic patient is enhanced by a knowledge of the quantity of albumin and carbohydrate in the diet.

5. A lowering of the carbohydrate intake in a severe case of diabetes from a total of 80 gm. to 55 gm. in twenty-four hours produces little effect upon the acidosis.

THE STUDY OF THE FUNCTIONS OF THE ALIMENTARY TRACT FOR THE DIGESTION AND ABSORPTION OF FOOD BY THE EXAMINATION OF THE FECES, IN CLINICAL WORK.

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THE function of the alimentary tract is the digestion and absorption of the food. Whatever portions of the ingested food mixture fail of absorption in the course through the tract become finally constituents of the feces and are excreted in this excretion. The constitution of the feces of an individual must, therefore, be to a certain extent directly dependent upon the quality of the function of digestion and absorption in the alimentary tract of that individual; that is, the proportion of food derivatives in the feces upon a definite diet should vary according to the integrity or disturbance of integrity of the function of the alimentary tract present. In view of these facts it is clear that the examination of the feces should serve us in medicine as a means of studying the condition of digestion and absorption of food in the alimentary tract.

The most accurate and comprehensive single method of investigation of the feces for this purpose consists in the quantitative analysis of the total proteid, fat and carbohydrate constituents of the daily fecal excretion. The principal elements of the ingested food which undergo digestion and absorption in the alimentary tract belong to these three classes of food material, — proteids, fats and carbohydrates. Where disturbance of function resulting in lessened utilization of food in the alimentary tract exists, larger quantities of one or all of these substances, according to the character of the disturbance, will appear in the feces than are present there under the same conditions of diet in the normal, and will increase the total content of feces in these products. This variation in the constitution of the feces in proteid, fat or carbohydrate constituents will, of course, appear in the results of quantitative analysis. If, therefore, any individual with a disturbance in the function of utilization of food substances in the alimentary tract is placed upon a fixed or " test " diet and his daily fecal excretion subjected to quantitative analysis of nitrogen, fat and carbohydrate, we can, by a comparison of the results of such analysis with standard results of the constitution of the normal daily fecal excretion under this test diet, determine the fact of the increase of the proteid, fat or carbohydrate (the nitrogen serving as an index of proteid content) which results from the disturbance of function present.

It is clear, then, that this method of the quan-

titative analysis of the nitrogen, fat and carbohydrate of the feces obtained under definite conditions of diet, since it determines for us the fact of the relative completeness of utilization of the food in the alimentary tract, must serve as a direct and comprehensive means of studying the condition of function of the tract. For it is this utilization of the food, its absorption, which is the chief end and aim, the final achievement, of the combination of all the functions of the alimentary tract; and the completeness of such utilization as evidenced in the quantitative analysis of the feces is the most absolute index of the functional capacity that we can have. The application of the method in any case, that is the subjection of the feces to quantitative analysis and the comparison of the results obtained with the standard normal results, gives us: 1, evidence of the existence of abnormal conditions of function; 2, evidence of the particular type of function which is disturbed, whether that of the utilization of proteid, fat or carbohydrate; and 3, the extent of the disturbance in quantitative measure.

It must be borne in mind in the use of this or any method of quantitative analysis of the food principles of the feces, that the results as regards the estimation of food derivatives are accurate, only for determining the *comparative* quantity of these substances present, the quantity found in a given case as compared with that present in standard normal cases under the same diet. These records, though they may give accurate

determination of the total fat, proteid and carbohydrate present in the feces, never represent accurately the exact amount of the proteid, fat or carbohydrate of the food which has escaped utilization in the alimentary tract. They represent this quantity of food derivatives plus whatever proteid, fat or carbohydrate of the feces is derived from other sources, as, for example, the tissues and secretions of the alimentary tract and the bacteria of the gut. That a certain amount of the nitrogen content and the fat content of the feces is always derived from these body sources is an undoubted fact proved by observations upon the feces of fasting individuals. Thus in the twenty-four-hour fecal excretion of the professional faster Cetti, Müller found 0.316 gm. of nitrogen, and 1.21 gm. of fat.[1] These findings must, of course, be attributed to the body excretions. Where food is taken it is not unlikely that the amount of such body nitrogen and fat is considerably greater, as more activity of secretion and more waste of tissue are present. Some carbohydrate substances are present in the constitution of bacteria, and it is possible that a portion of the carbohydrate of the feces determined by analysis is from this source.

The determinations of quantitative analysis are the estimates of total finding and do not distinguish food derivatives from body derivatives. In our study of the feces for the determination of the utilization of food substances we take it for

[1] Fr. Muller: Virchow's Arch., 131, 1893, Supplementheft.

granted that the proteid, fat and carbohydrate contents derived from the body are fairly constant in individuals upon the same diet. With this assumption our test is accurate for comparative work though it is not, as demonstrated, strictly so for absolute deductions as to the quantity of food derivatives. It is probable that this constancy is a fact in normal conditions. In abnormal conditions we cannot, of course, be sure of this fact. So in deducing the fact of the existence of a disturbance of the function of utilization of any special food, proteid, fat or carbohydrate, by the finding of an excess of this substance over normal in the feces in all cases, we are depending upon an assumption which may or may not be correct. We know that a disturbance of the function of absorption must cause an increase in the food content of the fecal excretion; but it is not equally a fact that an increase in the content in any one of the food principles means necessarily an increase in the quantity of this substance derived directly from the food. It may mean an increase in the unabsorbed food products or an increase of the portion of the proteid, fat or carbohydrate of the feces derived from body sources.

Practical consideration of the subject in the light of our knowledge of the physiology and pathology of the body would, however, make it appear fairly certain that this theoretical objection to the formulation of definite conclusions in regard to the condition of function of the alimentary

tract from the findings obtained from the use of this method, is of practical import only in respect to one branch of function, that of the utilization of proteid. It is a well-recognized fact that the inflammatory and serous exudates of the body, wherever found, contain considerable quantities of proteid or of nitrogenous substances derived directly from the blood and tissues of the body. The presence of such inflammatory or serous exudates in the intestines is a very common pathological condition, as, for example, in inflammatory affections of the intestinal mucous membrane and in serous diarrhea from any cause. In such conditions and in conditions of hemorrhage into the alimentary tract there can be no doubt that a considerable portion of the increase of the proteid and nitrogen content of the feces which occurs may be due to excess of body proteids, as distinguished from food proteids. In such cases we must, therefore, be very conservative in ascribing an increase in the nitrogen to deficiency of absorption of food proteids, that is, in concluding the existence of the disturbance of the function of proteid utilization from the results of nitrogen analysis in the feces. All that we can justly claim from the results of the application of this method in general is that one suggestion offered by the presence of an increase of nitrogen content of the feces is that of the existence of the disturbance of the function. If inflammatory conditions, serous diarrhea, or hemorrhage are present we can make no absolute deductions as to proteid ab-

sorption. This point is illustrated by Case II, reported on page 666 of this article. If these conditions can be excluded we can reasonably conclude that an increase in nitrogen indicates a disturbance in proteid function.

As regards the fats, our general knowledge of the physiology and pathology of the body would lead us to believe that an increase in the total feces fat of any extent from an increased excretion of body fat, as distinguished from food fat, would be at most an extremely rare occurrence and that it is a fairly safe plan of procedure in general work to ascribe a finding of a fat excretion above the normal limits to an increase of unabsorbed food fats. A similar statement can be made in connection with the carbohydrates of the feces. It is safe in this plan of study of function to take it for granted in the general run of cases that the quantity of body or bacteria carbohydrate of the feces is of insignificant amount and that an increase of carbohydrate content of any marked degree indicates disturbance of the alimentary tract in the utilization of carbohydrate. There is reason to believe that the analysis of the carbohydrates of the feces gives us in all probability in all cases an estimate of the utilization of the food substance which is too high. For it is an undoubted fact that a considerable breaking up of the soluble carbohydrates which pass the intestine unabsorbed occurs in the lower intestines and feces through the agency of the lower organisms present in the intestinal con-

tents. For this reason the quantity of unabsorbed food carbohydrate which gets into the feces and can be determined there as such is in all probability less than the total quantity of this substance which is unabsorbed in the intestinal tract. This fact does not, however, affect the validity of conclusions made from the presence of an increase in fecal carbohydrate.

The results of the application of this method of quantitative analysis of the test diet feces, though they aid us greatly in determining the fact of the existence of disturbance of function of the alimentary tract, and indicate the particular kind of food utilization which is disturbed, whether that of proteid, fat or carbohydrate, leave much unexplained in regard to the conditions of the details of functional activity which make up the combined function of the stomach and intestines for the utilization of food. A disturbance of function resulting in a decreased utilization may consist entirely of a decreased capacity of the organs for the digestion of food, any failure in absorption being secondary to this, or of a decreased capacity of absorption independent of the quality of digestion, or of a combination of both conditions. Either disturbance would result in a final decreased absorption of food products and, consequently, in an increase of fecal content of the food substance in question. The result of quantitative analysis is to tell us simply this fact of lessened utilization. It tells us nothing as to whether it is digestion or

absorption which is primarily at fault. To gain some insight into these details of function we must supplement our method of quantitative analysis of the total nitrogen fat and carbohydrate of the test diet feces by other methods of examination of the feces.

For the study of the question of digestion of the fats as distinguished from that of the final utilization of these products we must use the method of the differential quantitative analysis of the total neutral fat, total fatty acid and total soap of the feces.

The neutral fats of the food are, in the process of the utilization of fat in the alimentary tract, broken up by a process of digestion into fatty acids and glycerin. The fatty acid, or a portion of it, is then combined with the alkalis provided by the intestinal content to form soap. These final products, fatty acids, soaps and the remains of neutral fat. are then for the most part absorbed. Such portions as escape absorption pass into the feces. Any deficiency in the initial process of the utilization of fat, the splitting of the neutral fat, may, whatever the capacity of the intestines for absorption, result in the presence of a higher proportion of neutral fat in the total fat present than is found in normal conditions in the intestinal content, and presumably also in that portion of the intestinal content which gets into the feces. The normal proportion of neutral fat to the total fat content of the feces upon a definite test diet, once established

by experiment upon normal individuals, it is a simple matter by a comparison of the records of differential analysis of the feces of a given case upon the test diet with these normal records to determine whether or not the so-called digestion of fat is normal. If the proportion of neutral fat to the total fat content is excessive the existence of some disturbance of this digestion is suggested.

For the study of the digestion of proteids and carbohydrates we have the method of macroscopic and microscopic examinations of the feces under a definite test diet, devised and perfected by Schmidt and Strasburger.[2] These authors have found, as a result of a considerable amount of experimentation, that under the use of a definite test diet (known as the Schmidt and Strasburger test diet), containing a certain quantity of meat muscle fiber and a certain quantity of starch, the macroscopic and microscopic appearances of the feces in regard to meat remains and starch remains will vary, in accordance with whether or not the digestion of these forms of proteid and carbohydrate is normal or disturbed, in certain definite characteristics as to the quantity and condition of these remains, so that an observer, familiar with the characteristic appearance of the normal feces in these respects, can determine by macroscopic and microscopic examination in any given case under this test diet, whether or not any disturbance of

[2] Schmidt and Strasburger: Die Feces des Menschen, second edition, Berlin, 1905. Verlag von August Hirschwald.

the digestion of these proteid or carbohydrate substances exists. The feces findings in these special substances, muscle fiber and starch, are, of course, entirely independent of the condition of the function of absorption present. They vary with digestion whether absorption is normal or not.

This method does not, strictly speaking, provide a test for the digestion of proteid or carbohydrate generally. It does not, for example, give evidence as to the capacity for the digestion of egg, proteid, milk proteid, plant proteid or of dextrine or sugar carbohydrate. It does, however, serve as a test of the capacity of the alimentary tract to digest certain common forms of food proteid and carbohydrate, the form of carbohydrate being that which most requires digestion for its utilization in the body. The method, therefore, gives us valuable knowledge in regard to the condition of function of the alimentary tract.

This method of determination of the condition of function of the digestion of meat, muscle proteid and starch by microscopic examination of the test diet feces as outlined by Schmidt and Strasburger is as follows:

The individual under observation is given the following diet for a period of three days:

In the morning: 0.5 liter milk (or if milk does not agree, 0.5 liter cocoa, prepared from 20 gm. cocoa powder, 10 gm. sugar, 400 gm. water and 100 gm. milk); to this add 50 gm. zwieback.

In the forenoon: 0.5 liter oatmeal gruel, made from 40 gm. oatmeal, 10 gm. butter, 200 gm. milk, 300 gm. water, 1 egg (strained).

At noon: 125 gm. chopped beef (raw weight) broiled rare with 20 gm. of butter, so that the interior will still remain raw; to this 250 gm. potato broth (made of 190 gm. mashed potatoes, 100 gm. milk, and 10 gm. butter).

In the afternoon, as in the morning.

In the evening, as in the forenoon.

The feces of the second or third day are collected, thoroughly mixed by stirring, and examined macroscopically and microscopically.

For the examination a portion of the feces is diluted with water, ground lightly in a mortar and spread out in a thin layer on a black plate.

Macroscopic masses of meat remains are identified under the microscope.

The character and quantity of the muscle remains is determined by microscopic examination.

The character and quantity of starch remains is studied under the microscope.

For the purpose of the microscopic study of starch remains a drop of iodine and potassium iodide solution (Lugol's solution) is mixed with a portion of the feces, and the mixture placed on a slide under a cover slip and examined.

According to the authors, no free undigested granules of starch staining a deep blue with the iodine are found in normal conditions under the test diet. Some potato grains with starch enclosed in cellulose may be present.

This comprises the list of the methods of examination of the food constituents of the feces which have been proven useful for the study of the conditions of function of digestion and absorption of food products in the alimentary tract in practical medicine.

To make a comprehensive study of function in any case, a determination of the condition of both the functions of digestion and absorption of the three principal classes of food material in the alimentary tract, the investigator must utilize all the methods described, making a microscopic examination of the feces, after the method of Schmidt and Strasburger, for the purpose of studying the functions of muscle and starch digestion, a differential quantitative analysis of the neutral fat, fatty acid and soap in the diet feces, to study fat digestion and a quantitative analysis of the total nitrogen, fat and carbohydrate of a test diet feces to determine the general condition of function of absorption of proteid, fat and carbohydrate.

This process involves considerable labor and a certain amount of knowledge of microscopic and chemical technic. The only method among those included, which is simple enough in its application to recommend itself for the use of the general practitioner in the study of his cases, is the method of macroscopic and microscopic examination as outlined by Schmidt and Strasburger. And this method gives only a very partial information in regard to the general condition of function of

the alimentary tract, determining only the condition of function of digestion of muscle fiber and the digestion of starch, and possibly in some cases something in regard to the utilization of fat, and revealing nothing in regard to the total utilization of proteids and carbohydrates generally.* In spite of the difficulties of the subject, however, this plan of the examination of the feces by the combination of methods described as required for the purpose of studying the condition of function of the alimentary tract for the utilization of food should be more generally utilized in medicine. Since the knowledge gained by such clinical procedure cannot but be of great service in connection with the understanding and treatment of conditions of disturbance of the alimentary tract, diseases of the large glands of the tract, the liver and pancreas and abnormal conditions of nutrition generally.

A study of this subject of the investigation of the function of the alimentary tract by the exami-

* Schmidt and Strasburger, in their publications of the method of the study of the functional condition of the alimentary by the macroscopic and microscopic examination of the test diet feces, claim that this method in addition to its use for the study of the condition of muscle and starch digestion, has a further use in connection with the study of the condition of fat utilization. According to this claim, the study of the test diet feces by macroscopic and microscopic examination will reveal, by the character and quantity of the visible and recognizable fat remains present, whether or not the total quantity of fat excretion is normal or increased, and hence give to the observer an indication of the normality or abnormality of the condition of the function of fat utilization present.

That this method may give such indications as to the condition of function when great disturbance of fat function is present is an undoubted fact. But that the method is useful in point of its accuracy, for the determination of the normality or abnormality of the fat finding in the general run of clinical cases is, according to the experience of the authors of this article, a matter of much doubt. The authors have, therefore, omitted this method from their general method of examination.

nation of the feces has for some time been carried on in this laboratory. One branch of this investigation has consisted of the application of this method or combination of methods of the examination of the feces described as required for the comprehensive investigation of the condition of function of the alimentary tract to the study of a variety of cases, both normal and pathological, with the idea of determining the usefulness of the method in question for the general study of clinical cases.

For the accomplishment of such a systematic study it was necessary to fix upon a definite " test " diet which was suited to the use of all the various methods included in the general method of examination, and to make a collection of the results of the examination of the feces under this test diet in a number of individuals with a normal condition of function of the alimentary tract for use in comparison in the study of the various cases examined in clinical work.

Since the character of the findings in respect to both the quantity of proteid, fat and carbohydrate, and also the macroscopic and microscopic appearance of food remains in normal conditions of function vary in accordance with the quantity of proteid, fat and carbohydrate in the diet, and also with the particular form of the food materials making up this diet, it is necessary in an experiment of this kind to use in all cases a test diet of a definite constitution in the three food principles mentioned and containing definite quan-

tities of separate forms of food material, as meat, bread, milk, etc. As a necessary part of the combined method of investigation, that of the study of the microscopic character of the muscle and starch remains in the feces for the determination of muscle and starch digestion necessitates the use of the special Schmidt and Strasburger test diet; the work of these authors having proven that this diet was most adapted for this special object of research, it seemed advisable to adopt this test diet for general use in the application of the combined method of investigation.

The first set of experiments included in the investigation consisted in the collection of a record of the findings of the feces of normal individuals subjected to this required method of examination under this test diet. This preliminary publication of the work of the laboratory upon this subject consists of a report of this experiment.

For the purpose of the investigation a number of individuals in normal condition of nutrition and, as far as could be determined, in possession of a normal condition of function of the alimentary tract, were placed upon the test diet for a period of four days. The total fecal excretion of this period was collected. A specimen of feces obtained upon the third or fourth day of the régime was subjected to examination by the method or combination of methods described, viz., the quantitative determination of the total nitrogen, total fat and total carbohydrate; the quantitative determination of the total neutral

fat, total fatty acid and total soap; the macroscopic and microscopic examination of the feces in respect to the quantity and character of the muscle fiber remains and the starch remains present.† The results of this examination were tabulated in each case, the report of each case containing a record of the per cent of dried residue of the feces in nitrogen, fat and carbohydrate, a record of the proportion (per cent) of each of the three forms of fat substance to the total of all the fat present, and a record of the character and comparative quantity of the meat remains and of the starch remains discovered in the microscopic examination.

The number of individuals experimented upon was eleven. As it was desired to obtain normal records which could be used for comparison in the application of the method to all varieties of clinical cases, persons of all ages, children and adults, were included in the list of individuals examined. In the case of several of the individuals examined two sets of experiments were made at different periods to test the constancy of the findings in the same individual obtained at separate times.

The test diet used was that developed by Schmidt and Strasburger for the purpose of the study of certain functions of the alimentary tract in clinical work. (See page 657.) The twenty-four-hour diet included the following food materials: 1.5 liters milk, 100 gm. zwieback, 2 eggs, 50 gm.

† If a good movement of the bowels occurs on the first and second days or on the second day of the experiment, all later feces represent test diet excretion.

butter, 125 gm. beef, 190 gm. potatoes, 80 gm. of oatmeal.

The diet was administered in the manner advised by Schmidt and Strasburger, described on page 657 of this article.

The content of this diet mixture as computed by Schmidt and Strasburger after the tables of Koenig is as follows: Proteid, 102 gm.; fat, 111 gm.; carbohydrate, 191 gm.

The caloric value is 2,234 (raw calories).

An analysis of the total fat content of a mixture of this diet used in one of our cases showed a higher content of fat, viz., 120 gm.

The methods of quantitative analysis used for the determination of the total nitrogen, fat and carbohydrate, and of the total neutral fat, fatty acid and soap were the following: In preparation for this analysis the whole feces of a single day was thoroughly mixed in 95% alcohol.[3] This mixture was divided into three portions, — one for nitrogen analysis, one for fat analysis and one for carbohydrate analysis. For the nitrogen analysis one drop of sulphuric acid was added to the mixture of feces and alcohol and the mixture evaporated to dryness on the water bath.[4] The residue was removed to a mortar, pulverized and dried to constant weight at a temperature of 100° C.[5] The per cent of nitrogen present was then determined by the Kjeldahl process.[6]

[3] Poda: Zeitschr. für physiologische Chemie, 25, 1898, S. 353.
[4] Camerer: Zeitschr. für Biologie, 20, 1884, S. 355.

The determination of the total fat, and of the total neutral fat, fatty acid and soap, was made by the following process: [7] The mixture of feces in alcohol was evaporated on the water bath, pulverized, dried to constant weight at 100° C., cooled in a dessicator and subjected to analysis.[8] One gram of the dried residue was placed in a capsule and boiled for one hour in absolute alcohol, using the reflux condenser. The capsule was then transferred to a Soxhlet tube and extracted for twelve hours with chloroform. The combined absolute alcohol and chloroform extracts were mixed, evaporated to dryness, and the residue extracted in sulphuric ether. The sulphuric ether extract was filtered, the filter paper being thoroughly washed with ether, and the filtrate evaporated. The residue of this sulphuric ether extract was taken up in petroleum ether, the petroleum ether extract filtered, and the filtrate placed in a weighed dish and evaporated.

The residue of the original absolute alcohol and chloroform left after extraction with sulphuric ether was scraped up and, together with the filter

[5] Schmidt and Strasburger: Second edition, page 111.

[6] *Ibid.* p. 117.

The method used in our work was as follows: One gram of dried feces was heated with 20 ccm. of concentrated sulphuric acid to which 5 gm. of sulphate of potash and a few crystals of sulphate of copper were added, for three to four hours until the mixture was clear. To this mixture, diluted with 200 ccm. of water, enough sodic hydrate to give a strong alkaline reaction was added (50 to 100 ccm.) and the mixture distilled into a solution of decinormal sulphuric acid until all the ammonia was separated (one-half to one hour). The acid was then titrated with decinormal sodic hydrate solution, and the per cent record of nitrogen calculated from this finding.

[8] Blauberg: Experimentelle und kritische Studien über Saulings feces. Berlin, 1897.

In cases where much fat is present the preparation of the dried residue must be accomplished by the drying of the feces under low heat in a vacuum.

paper used for filtering the sulphuric ether extract and that used for filtering the petroleum ether extract, was placed in a capsule in the Soxhlet tube and extracted for four hours with petroleum ether. This petroleum ether extract was filtered and the filtrate poured into the weighed dish already containing the first petroleum ether extract. This combined extract in the weighed dish was then evaporated, the residue washed with warm water to remove fatty acids not belonging to the series of food fats, and after the removal of the water, dried at 100° C., and cooled in a dessicator in a vacuum until by alternate drying and cooling constant weight was obtained. The weight of the final residue was recorded as representing the quantity of neutral fat and fatty acid present in 1 gm. of feces.

Following this first step of the experiment, the estimation of the total neutral fat plus fatty acid, the residue of feces from which this had been extracted was analyzed for soap. The dishes used for the evaporation of the absolute alcohol and chloroform extracts from the first extraction were washed with boiling alcohol, and this alcohol added to twice its quantity of hydrochloric acid alcohol, consisting of a solution of hydrochloric acid in 95% alcohol of a strength of 3% hydrochloric acid. The capsule from which the neutral fat and fatty acid had been extracted was combined with the capsule extracted by petroleum ether in the Soxhlet tube in the first part of the process, the capsule made up of a mixture of the

scrapings of the residue of the original extract of absolute alcohol and chloroform left after extraction with sulphuric ether, and the filter papers used for filtering the sulphuric ether and petroleum ether extracts, in a new capsule, and this new capsule boiled under a reflux condenser for one hour in the above mixture of 3% hydrochloric acid and the alcohol washings of the dishes of the first experiment. The capsule was then transferred to the Soxhlet tube and extracted with chloroform for twelve hours. The hydrochloric alcohol and chloroform extracts were then evaporated separately and the residue in each taken up in sulphuric ether, the combined sulphuric ether extract filtered, the filtrate evaporated, the residue taken up in petroleum ether, and the process of extraction continued as described in the first part of the process. The weight of the final residue of this second extraction was recorded as representing the quantity of soap present in the 1 gm. of dried feces.

The process so far carried out gave us the total quantity of neutral fat plus fatty acid, and the total quantity of soap present in 1 gm. of dried feces. The sum of these two determinations, the quantity of neutral fat and fatty acid and of soap represented the total quantity of fat present in 1 gm. of feces (plus cholesterin).

To determine the separate quantities of neutral fat and of fatty acid present the residue of the first part of the process representing the sum of

these two factors was dissolved in sulphuric ether, this solution added to an equal quantity of absolute alcohol, and the acidity of the mixture determined by titration with a decinormal solution of sodic hydrate in alcohol using phenolphthalein as an indicator. By multiplying the number of cubic centimeters of decinormal sodic hydrate used by the coefficient 0.0284 — which represents the equivalent of 1 ccm. 1-10 normal sodic hydrate in stearic acid — the quantity of fatty acid present in the 1 gm. of feces was calculated. By subtracting the quantity of fatty acid thus determined from the quantity of neutral fat plus fatty acid previously determined, the quantity of neutral fat was estimated. This analysis gave us the total quantity of fat and the quantity of neutral fat, fatty acid and soap present in 1 gm. of dried feces. From these records the per cent of total fat in the dried residue of the feces, and the proportion of the total fat present in each of the three forms of neutral fat, fatty acid and soap were calculated and these final records tabulated.

Duplicate analyses of the total fat were made in several cases, using sulphuric ether for extraction in the Soxhlet in the place of chloroform. The ether extraction was run for sixty hours, the absolute alcohol and sulphuric ether extracts of the first part of the process, and the acid alcohol sulphuric ether extracts of the second part of the process were evaporated, the residues taken up separately in petroleum ether, the petroleum

ether extracts combined, and the method continued as already described.

The results of the two methods of extraction, that by chloroform, and that by ether, in the cases in which both methods were applied, varied very little. As a rule the results by the chloroform method gave a slightly larger quantity of fat. As experiment showed that the complete extraction by chloroform was accomplished in much less time than by ether, the chloroform method was adopted in routine, and the records given are those obtained by this method.

As described, both sulphuric ether and petroleum ether were used for solution of the fat obtained by the Soxhlet extraction. It was found that the extract obtained from the residue of the Soxhlet extraction, whether chloroform or sulphuric ether were used in this extraction, by the use of sulphuric ether as a solvent, was invariably larger than that obtained when using petroleum ether. If the extraction of the Soxhlet residue was first made by sulphuric ether, filtered, dried to constant weight and weighed, and this extract then treated with petroleum ether, the weight of the latter extract was invariably less than that of the former. If, on the other hand, the Soxhlet residue was first extracted with petroleum ether and the undissolved residue left after pouring off the petroleum ether treated with sulphuric ether, a further quantity of this residue, amounting sometimes to 10% of the total extract of fat present, would go into solution in sulphuric

ether. If this sulphuric ether extract were dried and extracted with petroleum ether a portion, but not the whole, would go into solution in petroleum ether. So that by any method of treatment the total sulphuric ether extract was larger than that of petroleum ether. As, however, it seemed clear as the result of experiment that the sulphuric ether solution contains some substances other than fat it was decided to take the extract from petroleum ether as the final record of the fat content. As, however, it was also clear that the quantity of fat substance which could be extracted by petroleum ether was greater where a sulphuric ether extract was first made and a petroleum ether extract made from this than where an extract from the Soxhlet residue in petroleum ether alone was made, it was found necessary to use first sulphuric ether and then petroleum ether in obtaining the final fat extract.[7]

DETERMINATION OF STARCH.

The method employed was Strasburger's‡ modification of the Volhard-Pflueger method.

The stool is dried, ground fine and dried again to constant weight in the dessicator. Two grams

[7] References in regard to method of analysis of fats: The general plan of the method follows that suggested by Müller for application in clinical work. Fr. Muller: Zeitschr. für klin. Med., 12, 1887, S. 101.

For extraction of the dried residue the method recommended by Rosenfeld for extraction of fat from tissue by chloroform was used. Rosenfeld: Centralbl. für innere Med., 1900, no. 33.

It is recognized that other substances besides fat are taken up from the feces by chloroform and ether, — such as cholesterin, coloring matters and the phosphorus fat lecithin. Hoppe-Seyler: Physiologische Chemie, Berlin, Hirschwald, 1881.

Petroleum ether was used for final solution of the fat because as proven by our experiment it takes up less matter other than fat than sulphuric ether. The final residue obtained by the method recorded as total fat consists actually of true fat plus lecithin and cholesterin.

are accurately weighed and placed into an extraction flask of about 300 ccm. capacity: 100 ccm. of 2% HCl in distilled water are added and the whole boiled for one and one-half hours with a reflux condenser. After cooling, NaOH is added till the reaction is almost neutral, care being taken to retain a faint acidity to litmus. This is filtered rapidly through a hardened folded filter and carefully washed with distilled water. The filtrate is placed in a measuring flask of 200 ccm. capacity and distilled water added to the mark. Of this filtrate 50 ccm. are placed in a wide beaker of about 300 ccm. capacity and 60 ccm. Fehling's solution and 35 ccm. distilled water added. It is covered with a watch glass and suspended from a ring stand in the water bath in such a way that the contents is about 1 cm. below the surface of the water in the bath. It is essential that the water in the bath be boiling vigorously from the time that the beaker is placed in it till it is removed. After exactly thirty minutes the beaker is taken out and about 130 ccm. of cold distilled water are added. The content of the beaker is then filtered through a carefully prepared Gooch crucible. The fine precipitate of copper oxide collects on the filter and is thoroughly washed with water till the

‡ J. Strasburger: Arch. für die Gesammte Physiologie, vol. 84, 1901, p. 173.
A. S. Schmidt and J. Strasburger: Die Faeces des Menschen. Berlin, 1901. p. 165.
E. Pflueger: Arch. für die Gesammte Physiologie, vol. 69, pp. 416–414, 423–430, 437, 439–442, 468–471.
Bickel: Arch. für die Gesammte Physiologie, vol. 75, p. 248.

wash water is no longer alkaline. A rubber tipped glass rod is useful in collecting the copper oxide that adheres to the side of the beaker. The Gooch crucible is placed on the clean suction flask and a few ccm. of HNO_3 (S. P. 1.2) are added. The crucible is covered with a watch glass to prevent loss through foaming. When all the acid has dropped into the flask without the aid of the pump the crucible is thoroughly washed with water under suction. The filtrate is placed in a porcelain evaporating dish and about .5 to 1 ccm. concentrated H_2SO_4 added, and the whole evaporated on the water bath until all the HNO_3 is driven off. The residue, which consists of crystals of $CuSO_4$, is washed with a little distilled water into a measuring flask of 300 ccm. capacity. Concentrated Na_2CO_3 is added till all the acid is neutralized and a permanent precipitate appears. Then 50 ccm. saturated H_2SO_3 are added. A clear greenish-blue solution results, which is heated to the boiling point and immediately titrated with $\frac{n}{10}$ KCNS till the color has entirely disappeared. The solution is allowed to cool and water added to the 300 ccm. mark. After thoroughly shaking it is filtered clear and 100 ccm. measured with a pipette into a beaker and 50 ccm. HNO_3 C. P. (S. G. 1.2 — free from HNO_2) and 10 ccm. saturated ferric ammonium alum are added. A deep red color appears; $\frac{n}{10}$ $AgNO_3$ solution is carefully added from a burette until the cherry-red color gives way to an orange red. The amount of $\frac{n}{10}$ $AgNO_3$ solution used is

multiplied by three and deducted from the number of cubic centimeters of $\frac{n}{10}$ KCNS used and the result indicates the amount of the copper bound by the CNS. One cubic centimeter $\frac{n}{10}$ KCNS equals 6.32 mg. copper. The corresponding sugar value is found by reference to Pflueger's table and multiplied by the factor 0.94 (Soxhlet, Linter, Duell)§ to obtain the amount of starch.

In the method employed by us we have substituted the Gooch crucible for the asbestos filters of Pflueger. The crucibles must be carefully lined with long fibered asbestos in the usual way, and care must be taken to obtain an even coating, which is firm enough to withstand considerable pressure, but not so thick that it will be clogged with copper precipitate. If properly constructed the entire filtration takes from one quarter to a half hour. We have found that it is easier to obtain satisfactory results with the Gooch than with the funnel filter of Pflueger. The end point of titration with the ferric ammonium alum, however, is not easy to determine, and a number of estimations were made with sugar solutions of known strength to serve as a comparison with the starch determination.

The total weight of the dried residue of the specimen of feces used was represented by the sum of the weight of the dried residue of the three portions of the feces used, the nitrogen portion, the fat portion and the carbohydrate portion. This was recorded in each case.

§ Chemisches Centralbl., 1891, p. 733.

These records of the weight of dried residue do not in many cases represent the average daily excretion of the individuals under the test diet. In some cases the quantity of daily excretion varied within wide limits, in others this quantity of fresh feces was fairly regular upon each day. In the records of the cases in which the whole fecal excretion for the four days of experiment was obtained and reduced to dried residue a record of the average quantity of dried residue per day for the whole experiment is given, in addition to that of the specimen of the third or fourth day upon which the analysis was made.

In tabulating the quantities of the total nitrogen, total fat and total carbohydrate contents of the feces in our tables the records are given in per cent of dried residue.

It may be urged that such per cent records do not represent good data for judging the total utilization of food substances in the alimentary tract. That the record of the total amount of nitrogen, fat or carbohydrate contained, in the daily excretion on the test diet, the grams per day, is the proper record to serve as an index of food utilization.

This is true, and if it was the object of these records to estimate this fact of absolute daily utilization of the food products, such records would have to be used. The object of our method is not, however, to determine the actual figures of utilization of the food, but to obtain comparative records of the feces content and

through these of the comparative condition of function in individuals under examination.

The results of our experience with the subject have led us to believe that, under the conditions which obtain for the performance of this method of the study of the function of the alimentary tract as applied in general work in clinical medicine, these per cent records of the nitrogen, fat and carbohydrate content of the feces are more serviceable for use as comparative records, as indications as to whether or not the functions studied by our method are normal or abnormal, than actual records of the total daily fecal excretion of nitrogen, fat and carbohydrate in grams per day.

The reasons for this conclusion are given in the following statement of facts and discussion of the subject. To obtain accurate records of the average daily excretion of nitrogen, fat or carbohydrate in an individual upon a test diet the whole fecal excretion of three or four days must be collected and the determination made from this mixture. By giving carmine with the food at the begining and end of the test diet régime an accurate collection of the test diet excretion for a period of days can be made.

The collection of feces in this way necessitates an amount of observation and labor which makes the method impracticable for ordinary clinical work. It is, however, practicable for the physician to place his patient upon the test diet and, without undue labor or excessive management as

to precaution, obtain a specimen of feces representing the excretion of the third or fourth day of the régime, which he can have analyzed.

The collection of the whole excretion of the four days of experiment should, of course, always be attempted. In performing the experiment, however, in practice it is often very difficult where we trust to the patient to accomplish this object. Frequently, as in some of our cases, there will be no movement for two days and a large one on the two succeeding days. Or there will be two very constipated movements of much less than normal size on the third and fourth days. Or one stool will be obtained and diarrhea will then appear.

It is these practical difficulties which have led us to investigate what can be done with a per cent method of records of single day specimens for the purpose of the study of the subject in hand in general clinical work. The full metabolism experiment is certainly to be advised where it can be accomplished. For, as described later, the per cent records may, in certain pathological cases, though they give us a part of our diagnosis, give very inaccurate results as regards the understanding of some of the functions.

The points which I am emphasizing are that this method of examination is, in the general run of cases, an accurate method for clinical work, and that it can be used in such work where the method of calculation of total excretion per day cannot be accurately used.

A record of the actual quantity of nitrogen, fat,

etc., of single daily specimens of feces in grams per day may or may not give a correct estimate of the average utilization of food products of the individual under the test diet. For the variation in the size of daily fecal excretion, the weight of the fresh feces or the dried residue of separate days under the experiment is very considerable. In our experiments, for example, the variation between the quantity of feces of the third day and that of the fourth day was not infrequently 40 gm. in weight of moist feces, or 7 to 8 gm. in weight of dried residue.

In some cases no feces was obtained on the second and third days, and a large excretion, 200 to 300 gms., on the fourth day, so that records of the findings of single daily excretions in grams per day would show extreme variations in the same individual or among different individuals, and could not possibly serve for average records of normal excretion of nitrogen, fat, etc., for use in the determination by comparison of these records with those of a given case, whether or not the utilization of these substances in our test case was normal or abnormal.

On the other hand, the proportions of nitrogen, fat and carbohydrate in each daily specimen of feces obtained under the test diet in any individual should be and are, as proven by experiment, fairly constant. These proportions are not dependent upon the size of the varying daily excretions, but represent the average excretion of the food substances.

The per cent records of a single daily specimen of feces, therefore, represent good data for estimating the proportional utilization of food substances in a given case as compared with that of another case, or with the average utilization record of normal cases. They are much more serviceable in this respect than records of total daily excretion in grams per day determined from examination of single daily specimens.

So unless regular metabolism experiments made by the analysis of the whole fecal excretion of the several days' period of test diet régime are done, the per cent estimations of single specimens of feces are the most accurate and most serviceable records for the purpose of our experiment.

Conclusions based upon such per cent records, both as to the variation in the extent of utilization of food substances, which occurs in different normal individuals and as to whether or not the utilization in a given case is normal or abnormal, are, then, in the light of our general knowledge justifiable.

Since this is so, and since the obtaining of records of this kind which are reliable for use in the formation of conclusions as to the relative condition of function in given individuals, is much more practicable in the pursuit of regular clinical work, than the collection of records of the total excretion of food substances in grams per day, which would be equally reliable for the formulation of such comparative judgments, we have adopted this method of per cent

records in the establishment of our collection of standard normal records for use in comparison in clinical work.

The records of a study of the separate daily specimens of feces of two individuals during the test diet régime, given in the following table, will serve as an experimental demonstration of these facts upon which the above conclusions are based, the fact of the constancy of the per cent records in separate daily specimens of feces of an individual, regardless of the quantity of fecal excretion of any separate day, which indicates that such records of a specimen of one day of a test diet régime represent the average per cent composition of the feces under the test diet, and the fact of the extreme variation which may occur in the records of total excretion of food substances in grams per day, owing to the variation in the total quantity of feces of the separate daily excretions.

As you will see by a study of table 1 the size or dried weight of the separate daily feces in the same case varies greatly. The quantity of nitrogen, fat, etc., per day varies with these quantities of feces and, as you can see by calculation of the results, varies greatly on separate days.

The proportions of nitrogen, fat, etc., in these separate feces are, however, fairly constant. They do not vary regularly with the quantity of feces or in proportion to this quantity.

In the use of these per cent records in the study of clinical cases as a means of determining the

TABLE I.

		Grams, weight of fresh feces.	Grams, weight of dried residue.	Nitrogen, per cent.	Nitrogen, grams in feces.	Fat, per cent.	Fat, grams in feces.	Carbo-hydrates, per cent.
Case I. — One daily excretion on each of four days of experiment.	Feces of third day,	70.2	19.4	5.29	1.025	21.2	4.1	6.81
	Feces of fourth day,	89.4	21.1	5.01	1.05	23.2	4.9	7.05
Case II. — Excretion of first and second day. None on third and fourth days, excretion on fifth and sixth days. Diet continued six days.	Feces of fifth day,	226	57	5.4	3.07	24.1	13.6	
	Feces of sixth day,	54	12.1	5.04	0.60	23.2	2.8	

TABLE II.

	Weight of feces, average per day.	Weight of dried residue per day.	Nitrogen, per cent of dried residue.	Nitrogen, grams per day.	Fat, per cent of dried residue.
Case of jaundice: Examination of mixed three-day excretion.	315 gr.	59 gr.	4.14 Normal average, 5	2.49 Normal, 1 gr.	52 Normal, 20–35
Case of pancreatic disease? Examination of single daily specimen.	297 gr.	58 gr.	6.81		48

relative degree of utilization present in a given case as compared with the normal, of determining whether or not the actual utilization of nitrogen, fat, etc., in this case is normal, or decreased by disturbance of function, it must be borne in mind that in any pathological case where the excretion of one food substance, nitrogen, fat or carbohydrate, is excessive, thereby increasing materially the total bulk of the stool and, so to speak, diluting the feces content of the two remaining constituents by the greater quantity of excess of its own substance, this method of observation, while it gives us an accurate indication of the presence of an excess of the particular substance in question, thereby enabling us to make a diagnosis of the disturbance of function present in this respect, does not give us accurate indications in regard to the condition of utilization of the two remaining substances.

The fact that the per cent of these remaining substances is normal, or even low, does not prove that the total excretion of these substances is not actually increased. This fact can be illustrated by the record of an experiment upon a patient with obstruction of the gall duct (see Table II). In this case the function of fat utilization was greatly affected, causing a great increase of the bulk of fat in the feces and consequent great increase in the total bulk of the feces with comparative dilution of the fecal content of nitrogen. Yet the total excretion of nitrogen in this case was actually increased over normal, as the calculation of the

average total excretion in grams per day reveals. The per cent of nitrogen was, however, low normal. In the second case, on the other hand, the per cent records suffice for the determination of the fact that both the fat utilization and the nitrogen utilization are abnormal, both excretions being increased, and no estimation of the average total excretion per day is necessary.

Whenever in clinical work the result of the examination of the single day specimen of feces giving the per cent record of nitrogen, fat and carbohydrate and the records of the weight of dry residue shows an increase in the per cent of one food substance over normal, at the same time increasing the bulk of the feces so that the weight of the dried residue is much over the normal limits, we cannot, strictly speaking, conclude accurately from the per cent records whether or not the utilization of the two remaining substances, which show a normal or low per cent, is normal.

Our examination by this clinical method has, however, determined for us the existence of a definite pathological condition of function and the nature of the function which is principally disturbed. We can, then, since we have determined the existence of a pathological condition, make an accurate estimation of the condition of functions for utilization of the other two food substances by ordering a complete three days' metabolism experiment with a determination of the total excretions in grams per day.

If, on the other hand, the result of our experiment shows a record of normal per cent findings, and a normal weight of dried residue, we have determined the question of the conditions of the functions of the alimentary tract by our clinical method and need go no further. Practically, the only two conditions in which our clinical method of per cent records plus the weight of the dried residue fail to give us accurate determinations in regard to the utilization of all three classes of food substance and thus possibly necessitate the use of the more complete method in the study of the case, are conditions in which the function of fat utilization is seriously disturbed or conditions where the daily excretion of feces is on the average abnormally large, as represented by the weight of dried residue.

In the first instance our method gives us our diagnosis of the disturbance of one function. If it is necessary for the understanding of the case to determine the condition of the other functions we can then do so.

In the second instance we may, of course, have a normal per cent of the various food substances and yet have an actual increase in the total quantity of one or all, that is, a less utilization of these substances than in the normal.

In such cases the record of the increased quantity of dried residue, if such increase is found to be a fact, by obtaining the average of this factor for the days of the experiment, indicates to us, unless we have some affection of the intestine, such as

hemorrhage or inflammation with a large albuminous exudate present, that the function of utilization of food substances is disturbed, disturbed if the per cents of all three food substances are normal for all three, or if one substance is above the normal average though still within the limits of the normal, and the other two average findings disturbed principally for this special food.

The existence of this contingency described, the fact that where one substance in the feces and the total weight of dried residue are at the same time increased, the per cent records of single daily excretion in regard to the two remaining substances may not give reliable indications as to the normality or abnormality of these substances, does not, of course, affect the validity of our normal records as collected in this experiment for serving as indices of normal findings and the variations of findings in the normal.

It affects the value of these records for use in comparison in clinical work only in this respect: that in certain conditions, notably conditions of great excess of fat in the feces, we cannot use our records for comparison in respect to the normality or abnormality of the nitrogen and carbohydrate content.

It enables us, however, as well as by the more laborious method, to determine even in these cases the principal fact of a disturbance of fat function. It enables us in all cases where the proportion of the nitrogen, fat and carbohydrate

and the quantity of the dried residue are within the normal limits, to determine as well as by the more laborious method, the question of the normality of function.

The records of the normal characteristics of the test diet feces, under the method of examination and record described, collected as the result of 17 examinations upon 11 normal individuals, are given in the following table.

As the one object of the experiment was to provide and test by experiment a method of examination and record which could, where necessary, be used for the determination of the condition of function in cases in which single specimens of feces representing the excretion of one particular day of the experiment were obtained as well as in cases where it was possible to obtain the whole of the four days' expression, the records included are in all cases those of the examination of one separate day's excretion — that of the third or fourth day. [See Table III.]

The object of this experiment for the collection of a set of records of the characteristics of the feces of normal individuals as examined by this method for the study of the function of the alimentary tract was not only to give us some standard records for comparison in the use of the method in general work, but also to enable us to determine from the degree of uniformity in the characteristics of the feces of various normal individuals in regard to each of the particular finding of importance for the study of the sev-

eral functions of the alimentary tract, as the finding of proteid, of fat, of starch, etc., something in regard to the degree of usefulness of the method of general work. In the use of the method in any given case, we judge of the condition of any particular function as, for example, that of utilization of proteid, or that of the utilization of fat, in this case, by a comparison of our findings in this regard the total nitrogen, or the total fat of the feces with the normal finding. If the quantity of the nitrogen or of the fat is above the normal limits we diagnose disturbance of the function of proteid or of fat utilization respectively. If the quantities are within the normal limits, we judge that these functions are performing normally. Clearly, then, the degree of usefulness of this method of determination of the existence of normality or abnormality in regard to any particular finding by quantitative comparison of results is directly dependent upon the degree of uniformity or constancy of the particular finding in the normal results. If the results of our experiment upon normal individuals indicate that the capacity of function for the utilization of a given food substance on a definite diet is a matter of great variation in normal individuals, or in the same individual at different periods, then the usefulness of our method for making determinations of the normality or abnormality of function is limited to cases where marked disturbance of function exists.

For the increase in excretion of any particular

substance, following a disturbance of function of moderate extent existing in an individual of an average or more than an average capacity of function in regard to this special food substance might, in case that the variation in the substance was normally of wide extent, though it brought the total quantity to a figure abnormal for this individual, still leave the record of total quantity within the limit of variation of normal figures obtained from the study of a number of normal individuals. If, on the other hand, our experiment proves that the capacity of function of normal individuals for a given substance is constant in all cases, the limits of variation in the quantity of this substance in the feces of normal individuals under a test diet being very slight, then we may consider that the usefulness of our method extends to the diagnosis of degrees of disturbance of moderate as well as great extent, that is, that it is possible from our findings by the method, in a great majority of cases, to say definitely that a given function is normal or disturbed.

Let us now go over the records of our study of normal individuals to determine what these records show in regard to this question of uniformity of findings of the various excretions upon the determination of which our judgment in regard to the condition of the various functions studied by this method depends; that is, to determine the verdict of the experiment as to the degree of usefulness of the method of study in regard to

each of the functions of the alimentary tract.

The findings of meat remains, the muscle fiber, as revealed by the microscopic examination of the feces which serve as an index of the capacity of function of the individual to digest meat proteid in our experiment, showed great uniformity in all the normal individuals examined. The findings in children and adults were practically the same. From the definiteness and constancy of this finding in the normal, it would appear that it would be possible for any observer familiar with the normal finding to determine in any given case whether or not the finding was abnormal and thus to diagnosticate where it existed the presence of a disturbance of digestion of meat.

The records of nitrogen excretion, which serve as the index of proteid utilization in our experiment, were as follows:

Average finding in 17 examinations upon 11 individuals,	4.98%
Minimum finding in 17 examinations upon 11 individuals,	4.41%
Maximum finding in 17 examinations upon 11 individuals,	5.40%
Extreme variation of all findings,	0.99%
„ „ found in one individual,	0.41%

The findings in the three cases of young children average slightly higher than in the older children and adults, 5.05% with a minimum of 5% and a maximum of 5.4%, as against an average of 4.95% and a minimum of 4.41% and a maximum of 5.34% for older children and adults. This suggests that the utilization of proteid upon

this test diet is slightly less in young children than in individuals of greater age.

The findings of our experiment as regards the study of proteid utilization would, therefore, indicate that the capacity of function of normal individuals for the utilization of food proteid, under the conditions of diet in the experiment, is fairly uniform. From this fact it would appear that by the use of the method of investigation used in the experiment it should be possible to determine with considerable accuracy the existence or non-existence of any disturbance of the function of the absorption of proteid in any case under observation.

Examples of the possibilities of determination of the existence of a disturbance in the function of the utilization of proteid food by the method of study may be seen in the following records of two cases, in which the proteid finding was abnormal.

CASE I. Cancer of pancreas.

Microscopic examination: Great increase in quantity of muscle fiber over normal.

Total nitrogen, 7.81%.

CASE II. Enteritis with diarrhea: Microscopic examination showed quantity of muscle fiber normal, evidencing normal function of digestion of this proteid.

Total nitrogen, 8.05%.

According to our explanations in Table III, the increase of proteid in this case may be due to either an increase of food proteid or an increase

of body proteid (diarrhea being present). No absolute deduction as to the function of proteid utilization can be made.

The finding of total fat contents of the feces which serve as the index of the utilization of fat in our experiment were as follows:

Average finding of 17 examinations upon 11 individuals,	28.5%
Minimum finding of 17 examinations upon 11 individuals,	19.2%
Maximum finding of 17 examinations upon 11 individuals,	39.5%
Extreme variation of all cases,	20.3%
" " in a single individual (two examinations),	9.3%

If we contrast the findings in the three cases of young children with those of the older children and adults, we find that the average is much the same. That is, it appears that the utilization of fat under this test diet is equally good in children and adults.

The findings of our experiment as regards the study of fat absorption would therefore indicate that the capacity of function of normal individuals for the utilization of food fat under the conditions of diet used in this experiment shows a considerable variation. And this extreme variation is not a matter of one exceptional case — one extremely low finding and one extremely high finding. The maximum figure is approached in several cases and the minimum in several cases.

Since this is the fact it would appear that absolute determinations of the existence of disturbance of fat absorption could be made by

this method of comparison of the findings of the case under experiment with the normal findings only in cases where the normal excretion was large, so that a moderate deficiency in the absorption would increase the quantity of feces fat over the maximum normal limits, or in cases with a great deficiency of fat absorption. The variations in the quantity of fat in the normal are so extensive that it would appear perfectly possible for any normal individual whose capacity for utilization of fat was above the average to have a considerable deficiency of absorption of food fat, without increasing the quantity of feces fat above the normal limits. We can say in regard to any individual with symptoms of disturbance of intestinal function or of nutrition, whose feces show as the result of examination a fat content which is above the average normal; though still within the normal limits, that his feces findings suggest that a disturbance of the function of fat utilization may be a cause of his symptoms. But we can absolutely diagnose the existence of such a disturbance of fat function only in cases where the fat excretion transcends such maximum findings as are common in normal individuals.

This variation in fat content of the feces in the normal individuals on any definite diet is a well recognized fact. Thus v. Noorden found in the same individual upon the same diet a daily variation of from 0.5 to 4.5 gm.[9] It is clear that

[9] v. Noorden: Lehrbuch der Pathologie des Stoffwechsels, Berlin, 1893. sup. 7, S. 33.

such a variation would show equally in results obtained by actual calculation of the average daily excretion in grams per day as by those of this per cent method of calculation.

The findings in regard to the proportion of neutral fat in the total fat content of our feces, which serve as the index of the digestion of fat in our experiment, indicate that the proportion of this substance to the total fat excretion is fairly constant in normal individuals. In no case was the proportion above one third of the total fat. The findings in this regard would indicate that the capacity for the digestion of fat in normal individuals under the diet given was fairly uniform. The method of examination should, therefore, enable us to determine the existence of any considerable disturbance in this function.

The records of carbohydrate excretion, which serve as the index of carbohydrate utilization in our experiment, were as follows:

Average finding of 7 individuals,	8.01%
Minimum „ „ 7 „	6.39%
Maximum „ „ 7 „	11.2%
Extreme variation in all cases,	4.81%

The variation found in these normal findings for carbohydrates is, if we take the minimum and maximum records, very considerable in proportion to the quantity of carbohydrates present. A further study of the records, however, reveals the fact that a discrepancy from the common finding exists only in the cases of the two young children examined, the findings of the older

children and adults showing a fairly uniform character. The findings in the two children are both much higher than in the other cases, but are very similar to each other. The suggestion of this showing of our experiment is that the utilization of carbohydrates upon this diet is less good in younger children than in older persons. In using this method of examination for the study of function in the general run of clinical cases, therefore, we must use two separate sets of normal records for comparison, — one for young children and one for adults. If this course is followed, it would appear from the results of our experiment that the method provides fairly accurate means of determining the existence of any considerable disturbance of the function of utilization of carbohydrates, since the records obtained in normal individuals of the same general class as to age are fairly uniform. The number of observations made in regard to this point is, of course, too small to justify a decided statement to this effect. But as far as these records go this is the evidence: the extreme variation of the 5 cases of older children and adults being only 0.71%, the minimum finding 6.39%, and the maximum 7.1%, the average 6.78%, while the two cases of young children show records of 11% and 11.2%, respectively.

The finding in regard to starch remains as revealed by the microscopic examination of the feces, which serves as the index of starch digestion in our experiment, showed marked uni-

formity in all the normal individuals examined. The result of our experiment upon this point convinced us that under the Schmidt and Strasburger test diet the findings are so definite that any trained observer can determine in any case the existence of a normality or abnormality of this finding.

BLOOD CULTURES IN TYPHOID FEVER WITH COMMENTS UPON THE HOSPITAL TREATMENT.

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CONRADI [1] has recently found typhoid bacilli in the blood of a child four days before the first symptoms of the disease appeared, and he further records the discovery of typhoid bacilli in the feces of two individuals eight and eleven days, respectively, before they developed typhoid fever. These facts indicate that typhoid fever can be contagious in the prodromal and early stages of the disease, and in confirmation of this point Conradi has also been able to furnish statistical evidence. Of some six hundred cases of typhoid fever, eighty-five were shown to have acquired the disease by contact, and of this number forty-nine contracted the infection during the first week of illness of the primary case. It, therefore, follows that an early diagnosis of typhoid fever is absolutely essential if its spread is to be prevented.

The Widal reaction is rarely positive in the first

week, but it is present in about seventy-five per cent of the cases in the second week, and eighty-five per cent of the cases in the third week, thus becoming a more valuable test diagnostically the longer the disease lasts. Although the Widal reaction is present at some time or other in practically all cases of typhoid fever, it may persist for so short a time as to be overlooked. Furthermore it is not absolutely reliable, because it occasionally persists after a previous typhoid infection, and may even develop in the course of some other acute illness. The test represents an incalculable advance over previous methods of diagnosis, but Conradi's work on the early contagiousness of typhoid fever shows that earlier methods of diagnosis must be sought.

The cultivation of typhoid bacilli from the circulating blood appears to answer this requirement, for it has been convincingly shown [2] that it is possible to obtain a positive blood culture from over ninety per cent of typhoid patients during the first week of illness. The per cent of positive cultures falls very rapidly as the disease progresses, varying according to different observers from fifty-seven to seventy-three per cent in the second week, forty-three to sixty per cent in the third week, and from twenty-six to thirty-eight per cent in the fourth and fifth weeks. The blood culture method is, therefore, pre-eminently advantageous for the early, and the Widal method for the late diagnosis of typhoid fever.

The technic was at first a bar to the general

adoption of this method, but the introduction of various bile media [3] by Conradi, Kayser, Meyerstein and others has greatly simplified the process. It was supposed that the blood used for the test must be removed from a vein to avoid contaminating organisms, but Conradi found that the blood taken from the ear [4] would do as well, and his observations have been confirmed by Peabody [5] working at the Massachusetts General Hospital. The Kayser-Conradi Typhus Galleröhre for the use of the general practitioner have been employed for some time in Germany, and similar outfits are now furnished by our own boards of health.

The difficulty of an early clinical diagnosis in typhoid fever was well illustrated this last summer by the admission and discharge diagnoses at the Boston City Hospital. During the last seven months of 1907, two hundred and fifty-one patients entered with the diagnosis of typhoid fever, but only one hundred and sixty-five of this number were given the same diagnosis on discharge. Errors in diagnoses were undoubtedly made by the physicians who sent the patients to the hospital, but any one who has followed a medical service for some months is aware of the mild fever cases of doubtful etiology which occur upon it, and will be ready to concede that if these had been seen throughout their whole course many new diagnoses of typhoid fever would probably be made.

It was with the purpose of testing the new cultural method, particularly in the early and

doubtful cases of typhoid fever, that our work was undertaken.

Technic. — Normal ox gall was collected in a sterile flask immediately after the death of the animal and then transferred to test tubes in quantities of 5 ccm. each. These were then sterilized for ten minutes at 100° C. on three successive days, but as contaminations with motile organisms occasionally appeared, the autoclave was later employed subjecting the media to a pressure of 10 lb. for ten minutes, the pressure reaching as a rule 18 lb.

The arm was prepared by a nurse or orderly who first scrubbed a broad area including and surrounding the elbow with soap and water, and then with 70% alcohol and finally applied a corrosive poultice for thirty minutes. The blood was invariably taken from the median cephalic vein, which, after the first few attempts, proved to be a simple procedure. We were surprised to find that it was often easier to puncture a vein which was not plainly seen, but was palpable, than a vein visible to the naked eye, but freely movable beneath the skin. The operation caused as a rule less pain than the removal of several drops of blood from the ear. It is far cleaner and allows one to obtain an abundance of blood which is entirely free from contamination. Its disadvantages are the time consumed in the disinfection of the arm with the consequent apprehension on the part of the patient, the risk of infection and the need of an assistant.

Five to ten cubic centimeters of blood were usually removed, and of this quantity 2½ ccm. were placed in each of the test tubes containing 5 ccm. of ox gall; a portion was also saved for Widal reactions and histological study. We found it of advantage to use two bile tubes. Thus, of twenty-one positive cultures eight times the bacilli were obtained from only one of the tubes after the first transfer, and in four of these eight cases one tube never showed a growth. The blood, after its transfer to the bile-enriching medium, was incubated for about eight to ten hours, and then four loops from each tube were transplanted respectively to two plain bouillon tubes. These were examined twelve hours later and of those thus examined five — 62% — were positive at this time. The growth in bouillon should be sufficient for the performance of a Widal test in less than twelve hours. In another series of cases we should use a greater number of loops of bile in the transfer. The bacilli were easily detected in the bouillon, which medium has this advantage over the other media that from it a Widal test can be made at once. Typhoid bacilli were obtained in twelve out of twenty-one instances on transfer to bouillon after twenty-four hours' incubation in the bile medium, not until after forty-eight hours' incubation in one instance, and only after seventy-two hours' incubation in three instances. Motility did not prove to be a safe guide in diagnosis and we preferred to first test the bacilli with a typhoid serum of known agglutinative power. The organisms

were invariably found in pure culture and their reactions easily tested. Transfers were always made to plain agar (not sugar free) and often to blood serum and glucose agar, but we soon found that if the bacilli grew upon one medium they grew upon all.

We did not have much success with the transference of the bile to dextrose agar, making at the same time a stab in order to determine its ability to form gas. This method should enable a positive diagnosis of the paratyphoid group to be made in twelve hours.

The total number of cases studied was forty-five. Fifteen of these patients were later shown by the absence of the Widal reaction and course of the disease not to have had typhoid fever. The blood of one of these patients showed a positive culture of staphylococcus pyogenes aureus, and this occurred at a time when a positive diagnosis of osteomyelitis had not been made from the physical signs, and while typhoid fever was considered the probable diagnosis. This was the only instance in which we encountered an organism other than those of the typhoid group. It shows that the bile medium may be useful for the detection of other organisms than Eberth's bacillus.

Cultures from the circulating blood showed the presence of typhoid bacilli in twenty-one out of thirty cases of typhoid fever. The number of cases is so small that conclusions are only justified when these cases are considered in connection with those of

other authors. For convenience we have classified them according to the week of the disease in which the culture was taken:

Week of disease.	Number of cases.	Culture: negative.	positive.
1	5	0	5
2	19	8	11
3	2	0	2
4	0	0	0
5	1	1	0
?	1	0	1
relapse,	2	0	2
Total,	30	9	21

In three instances in which we examined the blood in a relapse typhoid bacilli were found. It would thus appear probable that blood cultures would be a useful point in the differential diagnosis between relapses and complications.

Positive blood cultures are somewhat more frequently obtained in the severe than in the mild cases of typhoid fever. Kayser (*loc. cit.*) gives the following data:

Nature of typhoid cases.	Total cases.	Positive cultures obtained.
Very severe,	27	21 or 78%
Severe,	21	16 or 76%
Medium,	41	25 or 61%
Mild,	36	15 or 42%

The difficulty of classifying cases of typhoid fever in terms of severity is obvious. We have attempted to do it more from the general impression the individual made upon us than from any one arbitrary criterion. It would not be justifiable to draw far-reaching conclusions from such a small number of cases as we present in the following table:

Nature of Typhoid cases.	Total cases examined.	Positive cultures obtained.
Severe,	9	8 or 88%
Medium,	15	12 or 80%
Mild,	6	1 or 16%

We repeatedly attempted to prove that mild cases of fever entering the wards were of typhoidal origin, but almost invariably failed to do so. In only one such case, in fact, were we successful. There is no doubt but that better results would have been obtained if the mild cases had been examined earlier. The severe cases were examined on an average by the eleventh day, the cases of medium severity on the twelfth day, but the mild ones, on an average, not until the sixteenth day.

It is certainly only fair to state that as time went on our experience improved, and it is quite possible that an occasional positive case may have been overlooked in the first part of our work. Improvement in technic, of course, was bound to occur. The time saved in investigating a single case was easily reduced two thirds, so that we feel the blood culture method of diagnosticating typhoid fever can be introduced as a routine measure.

The organisms from nineteen of the twenty-one positive cases gave all the typical reactions for typhoid bacilli. The organism isolated from one of the patients, who clinically did not differ in type from the others, produced gas in dextrose agar, to a slight extent in plain agar and had a more diffuse growth on plain agar than was the case with the other organisms, but the initial acid-

ity in litmus milk persisted. This organism was uncommonly motile, shorter and of smaller diameter than the typical typhoid bacilli. It resisted clumping with the sera of many other typhoid patients except in a dilution of one to ten, and was not agglutinated even by the patient's own serum until thirty-three days from the onset of the disease, and only then in a similar dilution. This patient's serum also failed to clump the laboratory stock cultures of typhoid bacilli except in a dilution of one to ten. It also completely failed to clump the laboratory stock cultures of alpha- or beta-paratyphoid bacilli except in the same dilution. v. Hösslin[6] has recently reported cases of this character. This case illustrates the advantage which the cultural method of diagnosis has over the agglutinative reaction.

The organisms of another case gave all the positive reactions for typhoid bacilli except that after the initial acidity was produced the latter changed back to a deeper blue than before. The changes in the acidity of the milk produced by this case (Gay) as well as by the previous case (Roan) are merely qualitative reactions and do not determine the classification of the organism.

The following tables show the variations of these two organisms in acidity and gas formation with the different sugar media in comparison with typhoid and alpha- and beta-paratyphoid bacilli. Plain bouillon was used from which the sugar was removed by the colon bacillus. To portions of this were added one per cent of lactose,

saccharose, mannite, dextrin, maltose, galactose and dextrose. The fermentation tubes used were those devised by Theobald Smith to whom we are indebted for many suggestions.

TABLE OF ACIDITY AFTER INCUBATION FOR FORTY-EIGHT HOURS.

Bouillon.	Control.	Typhoid.	Gay.	Roan.	Alpha-para-typhoid.	Beta-para-typhoid.
	No. of ccm. of $\frac{N}{100}$ NaOH used.					
Plain,	0.6	0.8	0.8	0.8	0.7	0.4
Lactose,	0.7	0.9	0.7	0.9	1.0	0.8
Saccharose,	0.8	0.7	1.0?	0.6	0.7	0.6
Mannite,	0.5	3.4	3.4	3.6	3.5	4.1
Dextrin,	0.6	0.8	1.3	1.2	1.3	1.0
Maltose,	0.6	3.3	3.3	2.8	3.0	3.6
Galactose,	0.7	3.4	3.6	2.6	3.1	3.8
Dextrose,	0.6	3.6	3.6	3.9	3.8	4.5

TABLE SHOWING GAS FORMATION AFTER FORTY-EIGHT HOURS' INCUBATION.

Bouillon.	Control.	Typhoid.	Gay.	Roan.	Alpha-para-typhoid.	Beta-para-typhoid.
Plain,	0	0	0	0	0	0
Lactose,	0	0	0	0	0	0
Saccharose,	0	0	0	0	0	0
Mannite,	0	0	0	+	+	+
Dextrin,	0	0	0	0	0	0
Maltose,	0	0	0	+	+	+
Galactose,	0	0	0	+	+	+
Dextrose,	0	0	0	+	+	+

From the quantitative results shown in the above tables, it is evident that Gay's organism agrees well with the typhoid organism, except that it produces a higher acidity in dextrin bouillon. In the table showing gas formation it corresponds throughout with the typhoid.

Likewise, it will be seen that the organism obtained from Roan agrees with the paratyphoids

in acidity, especially alpha-paratyphoid, with which the greatest difference is but 0.5 ccm. in galactose bouillon. In gas formation this organism is identical with the paratyphoids.

Control tests were invariably made in the gas formation and acidity tests and were repeated until constant results were obtained.

HOSPITAL TREATMENT OF PATIENTS WITH TYPHOID FEVER.

Typhoid fever caused nearly six times as many deaths in Boston during 1907 as it did in Munich during 1906, yet the two cities have about the same population. Other cities in Germany and England also show much less typhoid fever than does our city. The record is still more unfavorable if we go farther back, because the year 1907 showed the smallest typhoid death-rate which Boston has so far attained.

The recent lowering of the typhoid death-rate has been brought about in this vicinity chiefly by hygienic measures of a general nature — such as closer inspection of water, milk and shellfish, both by the city and state authorities. Little has been done to prevent contact infection which Conradi and others have demonstrated to be the source of about one-fourth of all cases. It would therefore appear that the prevention of contact infection was the factor which demanded especial attention here at this time.

Two opportunities are open by which contact infection can be avoided: first, the early diagnosis

of typhoid fever, and second, the detection of the bacillus carrier.

We have already alluded to Conradi's work which has shown that typhoid is especially contagious in the first week, and have demonstrated that by blood cultures an early diagnosis is possible. We are glad to again call attention to the fact that the Boston Board of Health is prepared to furnish blood culture outfits to those desiring them. Yet by this means only a portion of the contact infections can be avoided. The other source, the bacillus carriers, is entirely overlooked. With commendable energy, however, the State Board of Health has undertaken work along this line also and we undoubtedly shall hear much of it soon.

Fifty-five per cent of all diphtheria cases occurring in Boston during 1907 were treated in the South Department of the Boston City Hospital, and similarly fifty-four per cent of all fatal cases of typhoid fever which occurred in the city during the last five years were treated at one or the other of the three large hospitals. This is as it should be, because immediate contact infection is thereby reduced. That the practitioners in the city thoroughly approve of this course is shown by the large number of doubtful cases which they send to the Boston City Hospital, one third of the cases admitted with the diagnosis of typhoid fever in the course of seven months last year proving not to have the disease.

It is probable that the per cent of cases of ty-

phoid fever which will be treated in the large public hospitals will increase, and for several reasons. Typhoid fever is a very expensive disease in private life. The duration of the illness, the necessity for at least one and usually two nurses, the two daily visits of the physician, or even the need of a doctor in constant attendance, and the frequent calls for specialists of one description or another contribute to this end. The cost is not lowered by sending typhoid patients to a private hospital. These hospitals consider such patients so undesirable that they demand rigid isolation with absolutely no contact between them and the nurses of other patients. Indeed, several of the private hospitals absolutely refuse to admit typhoid patients at all, because the surgeons, who chiefly patronize such institutions, will not tolerate the chance of infection of their own surgical cases with typhoid fever. Only wealthy patients can enjoy the privilege of being treated for typhoid fever in a modern manner in their own homes.

The large institutions on the other hand are well adapted to the care of typhoid fever. They contain many wards, and it is a simple matter to so group the typhoid patients that infection of other patients and attendants can be reduced to a minimum. The isolation of typhoid fever patients in hospitals was provided for in Germany in 1905.[7]

Nurses should be protected during the care of typhoid fever patients in hospitals. In a former paper[8] we showed that nurses working in six hospitals in Massachusetts were eight times as liable

to contract typhoid fever as the ordinary citizen, and that hospital ward tenders under the same circumstances were thirteen times as apt to acquire the disease.

This last year (1907) forty-seven nurses in the State of Massachusetts have been thus attacked, while the total number of reported cases of typhoid fever in the state was two thousand three hundred and eighty-nine. Another year might not show that for every group of fifty typhoid patients a nurse developed the disease, but we think this not at all unlikely. Only ten of these nurses apparently contracted typhoid fever in private nursing, but thirteen of the hospital nurses, it is only fair to say, were infected by an early unrecognized typhoid case in a nurses' dining-room. It does not seem justifiable to expose twenty-three female nurses, fifteen male nurses and thirteen physicians on one day in the same institution to the risk of contracting typhoid fever from twenty-eight typhoid patients when a hospital possesses many wards and rooms into which these patients could be gathered and cared for by a third of the above number of attendants.

Isolation in separate wards is not by any means the whole story. Early diagnoses to determine when to isolate are essential. Fortunately, by the use of blood cultures, the early diagnoses are the ones most easily made. The possibility of making an early diagnosis probably decreases about five per cent a day after the first few days until well along in the second week when the Widal test be-

comes rapidly more and more positive. On comparing the dates upon which we made blood cultures with the dates of admission of these same patients to the hospital, we find that we lost on an average two days of time. This shows the need of such work being performed by those living in the hospital rather than by voluntary workers from outside. An early diagnosis demands much time, and allowance must be made for this in the organization of a medical clinic.

If it is really intended to stamp out typhoid from the community, patients should not be discharged from the hospital without a knowledge on the part of the health authorities as to whether they are typhoid carriers. The time at which the typhoid bacilli disappear from the stools and urine is a variable factor, and as far as the stools are concerned an uncontrollable one. It is perfectly feasible, however, to determine whether patients are free from bacilli. German regulations require isolation, when bacilli persist in the stools, until ten weeks after the beginning of the disease; after this period special rules are provided for those who may still be bacillus carriers. As yet no such regulation exists in Boston or Massachusetts, but a knowledge of the presence or absence of typhoid bacilli in the stools would exert much influence upon the date recommended for the discharge of a patient. Such work would demand much time, but it would represent a high standard of preventive medicine.

CONCLUSIONS.

1. Our data agree with those of investigators having much larger series of cases, namely, that typhoid fever generally can be diagnosticated in the first week by use of blood cultures, but that this method yields positive results in only about sixty per cent of the cases in the second week.

2. The typhoid bacilli are most easily obtained by blood cultures from the severest cases.

3. The typhoid bacilli were found in the relapse of typhoid fever in three individuals.

4. Typhoid fever is becoming more and more a disease to be treated in the larger public hospitals.

5. Isolation of typhoid fever patients in hospitals for the sake of other patients and particularly for the nursing staff is demanded.

6. Early diagnoses on entrance to the hospital and the detection of bacillus carriers before discharge are requisites in the present campaign against typhoid fever.

We wish to express our appreciation of the courtesy extended to us in our work by Dr. George B. Shattuck, Dr. John L. Ames and Dr. John Bartol who placed all their typhoid patients at our disposal, and to Dr. Francis H. Williams and Dr. Horace D. Arnold from whom we obtained special cases. The work would have been impossible without the co-operation of Drs. Rhea, Mabee and Bosworth of the Pathological Laboratory to whom we feel much indebted as well as to Dr. Adler for helpful suggestions.

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THE USE OF TUBERCULIN IN THE TREATMENT OF LOCALIZED TUBERCULOSIS EXCLUDING PULMONARY TUBERCULOSIS.*

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THE treatment of tuberculosis with the various products of the tubercle bacillus is nearly as old as the discovery of the specific cause of tuberculosis. A considerable mass of evidence has been collected concerning the therapeutic use of tuberculin in various ways. More recently, Trudeau and his associates at Saranac Lake have argued that the end to be attained was immunity against the tubercle bacillus. Some facts of animal experimentation also seem to favor this view. Those observers have reported a considerable series of cases of pulmonary tuberculosis showing the value of increasing doses of tuberculin. Sir A. E. Wright, of England, has utilized the theory of phagocytosis. He believes that in cases favorable for treatment, which are essentially localized tuberculosis, there is a deficient amount of opsonins, those substances in the blood which prepare the bacteria for ingestion by the leucocytes. According to his theory tuberculin acts

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by increasing the amount of opsonins, and the treatment should be controlled by the determination of the opsonic index.

It is not the purpose of this paper to discuss the theories of the action of tuberculin but to give the results obtained in a series of cases of localized tuberculosis. There were 25 cases, divided as follows: 9 cases of tuberculous adenitis, 4 cases of lupus vulgaris, 4 cases of tuberculosis of the genito-urinary tract, 3 cases of tuberculosis of the wrist, and 1 case each of tuberculosis of the knee, tuberculosis of the spine and pelvis, tuberculous sinus, tuberculous fistula in ano, and erythema induratum. As far as known no cases of pulmonary tuberculosis are included. In the early cases the opsonic index was determined as a routine, as a rule, twice a week. Of the cases included in this list, the opsonic indices were followed in 9 for varying lengths of time during the treatment. Seven were followed for over four months. Four cases (I, II, XI and XIII) showed an opsonic index of 1 or above, at two or more observations at the beginning of treatment. According to the rules laid down by Wright they were not satisfactory cases for treatment. However, they were not doing well at the time. Nevertheless, under treatment by tuberculin, 3 of the 4 showed a most satisfactory result. In 5 cases (X, XIV, XVIII, XIX and XXIII) the initial observations were distinctly below normal. All these 5 are classed as distinctly benefited. In none of the 9 cases was a marked tendency for the opsonic indices to follow any

particular curves noticed. As a rule, it should be said, however, that if a case was doing badly the index was often low, but not invariably so. The clinical manifestations were markedly more accurate. At first, attempt was made to re-inoculate at the time advised by Wright, that is when the opsonic curve was descending to normal. This was soon found to be impracticable, and for the last several months no opsonic indices have been determined in any of the cases under treatment. Cases which have been put under treatment since that time have apparently done as well as the others. The old cases have apparently done as well without the opsonic index as with it.

Dr. Roger Kinnicutt and the writer made some comparative opsonic index determinations, using different preparations of bacteria, white corpuscles and sera. In all the cases of which I have record, 10 in number, the greatest difference was in hundredths, using 1 as the standard. There were observations on a number of cases which were not treated. In all cases, at least four indices were determined over a period of two weeks. Twenty-three cases, obviously tuberculous, presented a fluctuating index beyond 0.8 and 1.2. Four cases, with the clinical diagnosis of probably a non-tuberculous disease, presented similar fluctuations. One of these is Case XXIII, in whom, it seems to me, we have a therapeutic diagnosis. Another was a case of a knee which was treated by request with vaccines of the gonococcus without change. A guinea pig inoculated with tissue

from that knee showed tuberculosis. Another, clinically, was a case of Hodgkin's disease, in whose sputum typical tubercle bacilli were subsequently found. The fourth was a patient with a mediastinal tumor who gave a positive tuberculin reaction. There were 5 cases of obvious tuberculosis, whose opsonic indices did not vary from normal limits. There were 3 cases in whom the clinical diagnosis of probable tuberculosis was made, whose opsonic indices did not vary from normal limits and who gave no tuberculin reaction. Five milligrams of old tuberculin were finally given in each case.

There were 3 cases of especial interest. The serum of an interne at the Massachusetts General Hospital was used on two occasions as control. Compared with my own serum his opsonic index was 0.6 and 0.65. The discrepancy was attributed to an error in technic. Two months later he had pulmonary hemorrhages. One case was seen in May, 1907, with a diagnosis of the tuberculous glands of the neck. Four different observations showed her opsonic index to range between 1.1 and 1.3. She was kept under observation but not inoculated, since at that time it was considered that she was manufacturing enough opsonins and ought to get well spontaneously. Her general condition improved. The glands of her neck became much smaller. She then passed from observation until February, 1908. At this time she presented enlarged glands in the left axilla, which were apparently

about to break down. She has been started on tuberculin but has been under observation only two weeks. The third case was a case of acute tuberculous pleurisy. Clinically the case was steadily failing and a bad prognosis was given. The opsonic index was continually over 1.2. After a period of three weeks, improvement set in and the disease was apparently arrested. The conclusions from the work on the opsonic index in connection with tuberculous disease are that the opsonic index has no value as a therapeutic indicator; that it may be of some value in diagnosis and prognosis, but it is certainly not reliable. Two observers will get approximately the same results.

In the cases about to be reported, no case has been under treatment less than four weeks. No case was taken unless it was doing poorly from the clinical point of view. In every case due attention was paid to the necessary doctrines of fresh air, food and general hygiene. Most of the cases, however, have continued their same mode of life without essential change. The diagnosis has been, of course, unfortunately clinical in nearly every case. Nevertheless, there seems to be doubt of diagnosis in no case, In every case the diagnosis was confirmed by at least one other observer.

The preparation used was tuberculin, B.E. The initial dose has varied from 1-10,000 to 1-1,000 of a milligram. The doses have been graded always to avoid any reaction, either con-

stitutionally or in the local lesion. In only 2 cases has there been any increase of dosage over 1-1,000 mgm. The dosage has been increased only when the case seemed to be standing still. There are a few cases which have been under treatment for nearly a year which are still improving on a dosage of 1-1,000 mgm. and have shown no signs of immunity. As far as known there have been no rises in temperature. On several occasions there have been constitutional reactions of headache and malaise in the twelve hours following inoculations. Occasionally, fairly well-marked local reactions at the site of the tuberculous lesion were seen. The most marked example was in Case XIX. A dose of 1-4,000 mgm. caused, first, a marked increase in a local lesion, and then breaking down and discharge, all within two days. Any such reactions were regarded as indications to decrease the dose. The inoculations have been given subcutaneously, chiefly in the back and abdomen. There have been no untoward effects at the site of inoculation beyond a trifling discomfort in some apparently susceptible cases. As a routine, cases have been inoculated once a week until the disease was apparently arrested. There was observed in no case any objection on the part of patients to the inoculation.

There were nine cases of tuberculous glands:

Case I. M., a young woman of twenty-three, gives a history of glands in the left axilla which were lanced

in 1899, glands in the right axilla which were first noticed in December, 1903. Glands in the neck were noticed in 1904. She has had three extensive operations on left side of neck. She was first seen April 23, 1907, at which time she presented large, disfiguring masses of glands on both sides of the neck. She was recommended for operation, but at my request operation was postponed in favor of a trial with tuberculin. She was inoculated with 1-2,000 mgm. of tuberculin, and since that time has been inoculated practically once a week and is now receiving 1-1,000 mgm. a week. At the present time she shows a slight fullness of the neck, but no visible glands. On palpation numerous hard small glands can be felt, none larger than a small cherry. There has been marked improvement of the general condition, but no gain in weight. At the present time she has been working for over two months. This case is regarded as arrested.

CASE II. S., a young woman of twenty, first noted "lumps" in both sides of the neck and both axillæ in November, 1905. She was first seen in May, 1907. At that time she presented numerous disfiguring masses of glands on both sides of the neck and in the left axilla. Operation had been advised, but declined. The initial dose was 1-3,000 mgm. She has received inoculations weekly up to the present time. For the past three months dosage has been 1-1,000 mgm. Present appearance: axillary glands are barely palpable. Small kernels are felt in both sides of the neck. There may be some visible fullness of the neck. There has been marked improvement of general condition with a gain in weight of ten pounds. This case is regarded as arrested.

CASE III. C., a girl aged fifteen, noticed a "lump" in the right side of her neck in May, 1906. Tonsillec-

tomy July, 1907. Oct. 15, 1907, a fluctuating mass was incised in the region of the lump before noticed. There was considerable induration and a persistent sinus which showed no tendency to heal. She was first inoculated Dec. 12, 1907. At that time there was a sinus leading to a mass on the right side of neck, size of small apple. She received weekly inoculations, increasing from 1-4,000 mgm. to 1-1,000 mgm. In three weeks the sinus was closed. At the present date she presents only a slight induration about the scar of the incision and no palpable glands. There was no change in general condition. This case is regarded as arrested.

CASE IV. C. S., a girl of eighteen, noticed a mass over the left clavicle, beginning in August, 1907, which steadily increased to size of a grape-fruit. There were no other palpable glands, and as she presented hoarseness and evidence of a mediastinal tumor it was thought advisable to operate. Operation, Dec. 28, 1907, and a few drams of tuberculous pus evacuated. She drained profusely for about a week and then stopped. The sinus persisted. On Jan. 17, 1908, she was inoculated with 1-3,000 mgm. of tuberculin. The discharge immediately again became profuse. She has had inoculations weekly since then. At the present time she is getting 1-2,000 mgm. There is a profuse discharge from the operation wound and a constant diminution in the size of the mass of tuberculous glands. This case is regarded as hopeful inasmuch as after the cessation of the discharge apparently a profuse discharge of necrotic material has been kept up by the use of tuberculin with a steady diminution in the size of the glands. The girl always appeared rugged, has remained at work, and shows no change in general condition.

CASE V. R., a young girl of ten, noticed glands in both sides of neck about one year ago. Incision for

" cold abscess " of neck in October, 1907. Tonsils and adenoids removed November, 1907. The tonsils on section showed no evidence of tuberculosis. She was first seen Dec. 14, 1907, when she presented numerous small glands in both sides of neck and two masses of glands the size of large walnuts in right side of neck, with a sluggish sinus leading to the upper one. She was given 1-4,000 mgm. and has been inoculated weekly with dosage increasing to 1-2,000 mgm. up to the present time. There has been marked diminution in the size of the glands. None are larger than small cherries. The sinus is practically closed. There has been a very marked improvement in the general condition with a gain in weight of twelve pounds in ten weeks. The weight before that time had been stationary for six months. This case seems to have been greatly benefited, with very good prospects of arresting the disease.

CASE VI. Sa., a man about thirty-five, presented in November, 1907, very large masses of glands in both sides of neck. The glands were somewhat tender. He refused to come for treatment except at two weeks' intervals. He was inoculated with 1-1,000 mgm. every two week for three months. At the end of the time the glands had diminished one half. The man kept at work and there was little change in his general condition. There seemed to have been some improvement in the condition of his neck and might suggest a hopeful prognosis if the man would consent to regular weekly inoculations.

CASE VII. F., a young woman of thirty, noticed glands in the left side of her neck six years ago. She had two radical operations five years ago. There was some little discharge from operation wounds. She took a long vacation and was apparently perfectly well

for three years, although she could always feel small "lumps" in her neck. About one year ago she began to have pain in left side of neck with increased size of glands. An abscess was opened on Oct. 7, 1907, which left a discharging sinus. On Oct. 19, she presented a few small glands in left side of neck and a discharging sinus, leading to a small indurated mass about halfway up the sterno-mastoid muscle. She was started on 1-2,000 mgm. which was increased slowly at weekly inoculations to 1-1,000 mgm. The sinus healed in two weeks. On the week of Jan. 17, 1908, there was some little pain in the neck, but was immediately relieved when four to five drops of pus discharged spontaneously. There has been no discharge since. At the present time no glands are palpable. There is only very slight induration about the operation wounds. There has been marked improvement in general condition, but no particular gain in weight. Of some interest is the fact that her catamenia, irregular for the past seven years and absent all last summer, has been practically regular since the inoculations began. This case is regarded as arrested.

CASE VIII. Ri., a woman of forty, has noticed some glands in the neck the size of English walnuts for a number of years. She has always been nervous but otherwise in good health. On Nov. 22, 1907, she presented a few small glands, the largest on the right side the size of an English walnut. Throat is negative. She was given 1-4,000 mgm. tuberculin which has been increased at weekly inoculations to 1-2,000 mgm. The glands are somewhat smaller but the marked change has been in the great improvement in the general condition of the patient. She is able to do her work more easily. She has no annoying symptoms from her glands which formerly troubled her

and made her nervous. This case is classed as benefited.

Case IX. B., a young woman of thirty, noticed a little over a year ago a " lump " in the right side of her neck which steadily grew larger. Ten months ago a large abscess was evacuated. The wound healed in two weeks, but below the scar a sinus has formed which from time to time has discharged a little. On Feb. 1, 1908, she presented a discharging sinus in her neck on the right side which led to an irregular mass the size of a small peach. She was given 1-4,000 mgm. and at weekly inoculations the doses have been increased to 1-1,500 mgm. After five inoculations the mass is hardly noticeable. The sinus discharged rather freely at first and is not yet healed. This case is classed as distinctly benefited in four weeks' time. Favorable outcome seems reasonable.

There were four cases of lupus vulgaris:

Case X. Mar., a woman of forty, has had extensive and increasing lupus of both sides of the face for the past seventeen years. She has faithfully been under treatment for ten years. This treatment has consisted of various caustics, x-ray, etc., without effect. She was first seen on March 12, 1907. At that time she presented many red, active, confluent, lupus patches over both sides of face, and left side of neck. These patches were raised in some instances one quarter of an inch. She has received weekly inoculations beginning at 1-2,000 mgm., increased to 1-750 mgm. at the present time. The present condition is that the left side of her face, which was most involved, seems quiescent. There has been very marked improvement in the appearance of her face. The lesions are no longer confluent, raised and red, and are much fewer. An occa-

sional single nodule appears. The color is a dark red. The scarring is very smooth and soft. Curiously, on the right side of the face, which was least involved, the result has not been so good, but the very marked improvement of the appearance of the face leaves no doubt of the great benefit derived from the tuberculin treatment. Whether this obstinate case will be ultimately cured is still an open question.

Case XI. E., a young woman of thirty, has had an extensive lupus of the nose and adjacent part of face and mucous membranes of the nose and mouth for eleven years. Under the most efficient treatment available the disease had steadily progressed. She was first seen in May, 1907. She was given 1-2,000 mgm. tuberculin, and was inoculated at weekly intervals for eight weeks with marked improvement. She was better than she had been at any time for ten years. Inasmuch as she lived so far from Boston she was given some tuberculin with instructions for inoculations by the local doctor. Improvement continued for a month. After that time the inoculations were given very irregularly, often two weeks going by without an inoculation. With the irregularity of the inoculations, improvement ceased, and after two months, treatment was abandoned. This case was not benefited, but the improvement with regular inoculations and the cessation of that improvement when the inoculations became irregular, seem to suggest a possible reason for the failure.

Case XII. H. L., a boy nine years old, had lupus of the wrist in 1901 and which began on the neck in 1902. Since 1904 he has been under treatment for Pott's disease. He was first seen April 23, 1907. At that time he had a lew lupus nodules in an extensive white scar of neck and chin. Over an area, 6 x 3 in., on the right wrist was a crusted lupus lesion. He was

inoculated at weekly intervals from April 24 to Aug. 17. The dose was increased from 1-2,000 mgm. to 1-1,000 mgm. On Aug. 17 he showed no lupus nodules and presented a smooth, white scar both on wrist and chin. He was given 1-1,000 mgm. at about two weeks' intervals from Aug. 17 to Oct. 25. At that time there was no recurrence. He disappeared from observation until Dec. 7. At that time a few new lupus nodules were starting on his wrist. He was re-inoculated, but has reported only at very irregular intervals since. At the present time he has numerous, new crusting lupus lesions in the scars of his neck and wrist. The boy lives among the most unfavorable environments. This case is one presenting a recurrence which it seems possible might have been averted had the boy reported regularly for inoculation. It certainly shows importance of close observation of cases and the necessity in some cases of continuing the inoculations after the disease is apparently arrested to avert recurrence.

CASE XIII. C. B., a boy eleven years old, has had an increasing patch of lupus vulgaris on his left cheek for seven years. This patch had slowly spread, despite the usual efficient treatment. He was first seen on April 23, 1907, when he presented a circular patch on his cheek about four inches in diameter. There were numerous red, active, new lesions. He was inoculated weekly from April 23 to July 28. The dosage was increased from 1-3,000 to 1-1,500 mgm. On July 28 the patch presented for the most part a smooth scar with only a small rim of ulcerated tissue on one half the circle. The physician in charge of the skin department stated that he was better than at any time during the four years he has been under observation. It was thought advisable to remove the small remaining rim of diseased tissue with curette and cautery. The boy

ther. reported not oftener than once in six weeks. He was seen on Feb. 5, 1908, when his lesion was entirely healed. Inoculations every two weeks had been urged upon the boy but he had not reported for them. Tuberculin seems to have had some part in the arrest of this disease. This case is in notable contrast to the preceding case, as this boy went without inoculations without recurrence. It should be stated, however, that the boy has better home surroundings; his general condition is far better and he shows no other lesions of tuberculosis.

There were four cases of tuberculosis of the genito-urinary system:

Case XIV. G. P., a man of thirty-three, has had pain and frequency of micturition since October, 1906. Since March, 1907, his urine has been cloudy and at times has contained clots. No other symptoms. The man is athletic and has worked hard. Rectal examination is negative. Urine contained pus, blood and tubercle bacilli. A guinea pig inoculated with the urinary sediment showed tuberculosis. Inoculations were begun on Nov. 25, 1907. The dosage was slowly increased at weekly intervals from 1-10,000 mgm. to 1-1,000 mgm., which he is now receiving. There has been little change in the local condition. The frequency is about the same. Pus and tubercle bacilli remain in the urine. There has been considerable improvement in the general condition. For some time previous to the inoculations his weight has been steady at 155. Without any other change, he now weighs 160, his best weight. He says he feels better than for years. This case is classed as doubtfully benefited. This case is a patient of Dr. Wilder Tileston, to whom I am

indebted for notes of the case and permission to include it in this series.

CASE XV. L., a young man twenty-one years of age, has noticed increasing frequency of micturition for the past year. When first seen on Oct. 31, 1907, he got up five times at night to urinate and urinated every one and a half hours during the day. There was considerable pain on micturition. His urine contained much pus. A guinea pig inoculated with the urinary sediment died of tuberculosis. On examination, his external genitals are normal. There is a nodule in the right lobe of the prostate. The right kidney is palpable and large, somewhat tender. On cystoscopic examination an injected bladder was found but no ulcers. He was not considered a case for surgical interference. Beginning with 1-4,000 mgm. the dosage has been increased on weekly inoculations to 1-1,000 mgm. At the present time he gets up either once or twice at night to urinate, and urinates during the day every two to three hours. There has been no pain on micturition after the first three weeks of treatment. There has been a gain of weight of about ten pounds. The man has kept at work. He says himself that he feels vastly better than at any time for two years. His comfort is apparently insured by stopping the frequency of micturition. His urine still contains the same amount of pus. This case seems benefited. The most conspicuous change has been the improvement in general condition.

CASE XVI. La., a young man of twenty, four years ago, had frequent and painful micturition with pus in the urine. For the last three years the pus has continued in the urine, but the frequency and pain have not been so marked. On cystoscopic examination the bladder seemed normal and pus was seen coming out

of the left ureter. At that time, September, 1907, the testicles and prostate were normal. On Sept. 10, 1907, a tuberculous left kidney was removed. The wound healed slowly. Beginning Oct. 17 he received weekly inoculations of tuberculin, the dose being increased from 1-3,000 to 1-1,500 mgm. The wound rapidly healed, but perhaps a more important feature than the tuberculin was the removal of several silk sutures. However, there was a gain of ten pounds in weight. The man is now at his maximum weight and working every day. He has no urinary symptoms. There is still microscopic pus in the urine and a few tubercle bacilli. On Feb. 7, 1908, his left testicle, which became swollen immediately after the operation before the tuberculin was given, again became swollen. His dosage was immediately cut from 1-1,500 mgm. to 1-3,000 mgm. At the present time the testicle is rapidly growing smaller. It cannot be definitely stated that this case was benefited by tuberculin. It seems probable that the use of rather large doses (1-1,500 mgm.) stirred up the process in the testicle. There has been, however, a marked improvement in the general condition.

Case XVII. Ma., a man of thirty-three years old, gives a history for the past six years of backache, and frequent, painful micturition, and pus in the urine. In August, 1906, a perinephritic abscess was drained, which left a persistent sinus. Since that time his frequency and pain in micturition increased and he no longer had control of his urine. He lost weight and was unable to do steady work. Cystoscopic examination showed a small injected bladder without ulcers. Testicles and rectal examination were negative. Tuberculin reaction was positive. Nov. 22, 1907, his left kidney was removed. Pathologically, it showed typical

appearance of tuberculosis. After the operation the frequency and lack of control of the urine persisted, and on Jan. 13, when first seen, he presented a large sluggish wound in his kidney region. Beginning with 1-4,000 mgm. he has received weekly inoculations up to 1-1,000 mgm. At the present time the wound has healed. He still has some lack of control of urine at night, but is able to hold his urine three or four hours in the daytime. There is no pain. The urine still contains pus and tubercle bacilli. The most marked change has been in the general appearance. In a little over six weeks he has gained fifteen pounds, and he is now doing a full day's work as painter. He states that after the inauguration of the inoculations of tuberculin he began to feel generally better and now is better than he has been for six years. While the local condition is apparently the same, there seems no doubt that the man's general physical condition has markedly improved.

There were three cases of tuberculosis of the wrist:

Case XVIII. Ch., a woman of forty-five, had had a painless swelling on the back of the right wrist for over a year. This swelling was removed at operation in March, 1907, and the mass proved to be tuberculous. She was first seen May 14, 1907. At that time she presented a clean scar with a considerable mass of indurated tissue about it. This mass had been increasing for the past three weeks with an increase of pain. She was given six inoculations of 1-1,000 mgm. at weekly intervals. At the end of that time there was no pain in the wrist, no induration, the motion was free. She was then discharged to go into the country. She was again seen in January, 1908, and had no symptoms or signs of recurrence. This case is re-

garded as probably arrested, although there might be some room for doubt as to the nature of the induration and pain coming on several weeks after the operation.

CASE XIX. G., a young girl of ten, gave a history of injury to the right wrist in December, 1906. This was soon followed by a painless swelling over the fourth and fifth metacarpal bones. She was treated by plaster fixation and Bier's hyperemia for two months without change. She was first seen April 8, 1907. At that time she presented a painless fluctuating mass the size of a golf ball on the back of her hand. On April 12 she was given 1-4,000 of tuberculin. The lesion promptly became larger, broke down within the next forty-eight hours. There were apparently well-marked constitutional symptoms also. The inoculations were kept up at ten-day intervals, the dosage being increased to 1-2,000 mgm. On June 21, the splint was omitted but the child did not keep the hand quiet. The induration of the back of the hand persisted. The splint was re-applied July 26. From that time on improvement was rapid. The splint was again omitted on Sept. 20. At that time there was present only a smooth scar on the back of the hand and considerable diffuse induration. She was then given inoculations at two weeks' intervals until Nov. 22, 1907. At that time very little difference between the two hands was noticeable. There was no deficiency in motion. Unfortunately, none of several x-ray plates were satisfactory. There were no inoculations after Nov. 22. The child was again seen two months later and the condition remained the same. This case is regarded as arrested.

CASE XX. M. M., a woman forty years old, who had pain and swelling in both wrists in January, 1906. Operation in September, 1906, when considerable

tuberculous material was excised from the anterior surface of both wrists. Tuberculin test was positive. She went into the country for six months. Considerable swelling still remained in both wrists but no pain. She started in work but the pain and swelling in the wrists increased. She was first seen Dec. 5, 1907. At that time she presented two clean scars in both wrists. In the left wrist there was a little swelling but no pain. There was fair motion of the left hand. The right wrist was markedly swollen. There was considerable pain, increased on motion and some swelling of the thenar eminence. There was marked limitation in motion of all the fingers. She has been inoculated at weekly intervals, the dosage being increased from 1-4,000 mgm. to 1-1,000 mgm. at the present time. There is now no swelling of the left wrist. The motion and strength of the left hand are apparently normal. The right wrist is still considerably swollen, although less so than at the inauguration of treatment. There is much less pain in the right wrist than at the beginning of treatment. There is marked improvement of the general condition, despite the fact that she does hard work in domestic service. This case is classed as doubtfully benefited.

There was one case of fistula in ano:

Case XXI. Bu., a man of fifty, has had a fistula on either side of the anus for four years. Has had several abscesses and several operations, including radical ones, for the cure of fistula, but the fistulæ have never been healed. He was first seen Oct. 20, 1907, when he presented large wounds on either side of the anus. Beginning with 1-2,000 mgm. of tuberculin he has had weekly inoculations and now is getting 1-1,000 mgm. The fistula has closed on one side and is appar-

ently healing in well on the other. There have been no untoward symptoms since the beginning of the treatment. Again in this case there has been marked improvement of the general condition.

There was one case of persistent sinus after operation for tuberculous peritonitis:

CASE XXII. B. G., a young woman of nineteen years, had an operation for tuberculous peritonitis six months ago, which left a persistent sinus. Beginning Feb. 6, 1908, she received tuberculin weekly beginning with 1-10,000 mgm. and increasing 1-10,000 every week. The environment of this case was changed for the better. Her general condition has been much improved. There has been marked gain in weight and strength. The discharge from the sinus is now spasmodic and averages much less. This case has been doubtfully benefited by the tuberculin.

There was one case of erythema induratum:

CASE XXIII. O'D., a young woman of twenty-five years of age, has had psoriasis for years. When a child she had some "scrofulous glands" of which she now has only the clean scars on both sides of her neck. For a number of years on both legs she has had varying sized lesions of erythema induratum which have ulcerated and formed scars. In that time her legs have never been free from ulcers. In the winter time the lesions are more numerous. She has had various treatments, including active specific treatment. There was some doubt concerning the diagnosis of this case, and Dr. Roger Kinnicutt observed her opsonic index for the tubercle bacillus from April 3 to Aug. 10. I am indebted to him for his notes and his permission to include the first part of this case. The first four

determinations of the opsonic index showed an index well below normal. She was then given tuberculin, starting in with 1-2,000 mgm. For several weeks there was no special change. Since that time the improvement has been steady. She now requires inoculation of 1-750 mgm. every seven days. On two occasions she has gone without inoculation for nine or ten days and very promptly on the eighth or ninth day new lesions have appeared. The last appearance of a new lesion was on Feb. 24, when she had been nine days without inoculation. Before that time she had been two months without any lesion, a thing which she does not remember to have happened since the onset of this disease. It is to be remembered also that she has more lesions in the winter time. This case is to be classed as distinctly benefited. It is of considerable interest, however, to note that the inoculations apparently have got to be kept up, although she has been under treatment for ten months, and at one time the disease seemed arrested. The psoriasis was unaffected.

There was one case of tuberculosis of the knee:

Case XXIV. J. B., a girl twenty-four years old, seven years ago had an excision of the right knee joint for tuberculosis. About Jan. 1, 1907, the left knee became swollen and somewhat painful on motion. There was no limitation in motion. She did not improve under best of general hygienic and local treatment. About Dec. 15, 1907, she had some pain localized to two red areas on the outside of the knee. On Jan. 9, 1908, she was given 1-10,000 mgm. She has had weekly inoculations to the present time, the dosage being increased 1-10,000 mgm. at each inoculation up to 1-1,000 mgm. On Jan. 25, she presented a sausage-shaped swelling along the outside of the knee joint,

which distinctly fluctuated and which apparently was outside of the knee joint. The swelling was incised on Jan. 31, and pus evacuated. After the evacuation of the pus, the knee joint itself was very little swollen and not at all painful on motion. There has been some constant discharge from the incision but no swelling of the knee joint. Under precisely the same conditions as before tuberculin was given she has gained seven pounds in weight. Before that time her weight had been stationary for three months. It is problematical how much the tuberculin had to do with the change in the picture. It seems possible that the formation of this localized abscess was hastened by its use. The general condition and the local condition, which had been at a standstill for several months, are now certainly better. This case is classed as doubtfully benefited.

There was one case of tuberculous spinal and pelvic caries:

Case XXV. V., a woman twenty-nine years old, had, one and a half years ago, a left ilio-psoas abscess which was opened in March, 1907. She was in a plaster cast for some time. This ilio-psoas abscess has continued to drain. She presented a rigid back, but no knuckle. She came under observation Oct. 2, 1907, and was running a continuous temperature. She received 1-3,000 mgm. on Nov. 3, which was increased, by weekly inoculations to 1-1,000 mgm. on Nov. 24. The temperature came down. The discharge increased, but on Dec. 1, 1907, a fluctuating mass appeared over the crest of the right ilium, which increased in size with variations in temperature. The abscess was opened on Jan. 2, 1908. At that time apparently bare pelvic bone was felt. The temperature still showed

wide excursions. On Jan. 16, 1908, she was again given tuberculin, this time with the initial dose of 1-10,000 mgm., which was increased at weekly inoculations 1-10,000 mgm. to 1-1,000 mgm. Since the second inauguration of tuberculin the temperature has drifted to normal and there has been some improvement in the general condition. The history of this case suggests the possibility that the tuberculin stirred up increased suppuration as evidenced by the formation of the second abscess. There seemed to be some slight improvement in the general condition. On the whole it cannot be said that this case received any benefit from the inoculations of tuberculin.

Of course, too short a time has elapsed to draw any permanent conclusions from the results as seen in this very small series of cases. Many of the cases are still under treatment. Experience also has shown the fallacy of definitely designating any case of tuberculosis as cured, no matter how long the interval of quiescence. The following conclusions, however, seem justified. Of 25 cases of tuberculosis localized elsewhere than in the lungs, treated with tuberculin, B. E., 6 cases were classed as arrested; 12 as distinctly benefited; 5 as doubtfully benefited; and 2 as uninfluenced by tuberculin. The most striking feature is that practically all of the cases showed a marked gain in a general condition, thus enabling them better to combat the local disease. The local condition was certainly markedly benefited in the cases of tuberculous glands and lupus. In the cases of genito-urinary

tuberculosis, while there was some amelioration of the local disease, on the whole there did not seem to be much change. The use of tuberculin apparently has to be continued over a long period of time. It does not prevent relapse. While the opsonic index may be of some value in diagnosis and prognosis, it seems to be of no value as a therapeutic indicator. The dosage should be small. The initial dose is from 1-10,000 to 1-4,000 mgm. On few occasions is it necessary to give over 1-1,000 mgm. Any marked reactions are to be carefully avoided. The best interval of inoculation apparently is one week. Regularity of inoculations is essential. The routine use of tuberculin is simple and should be accompanied by no discomfort on the part of the patient. In no case apparently was any lasting injury caused by the use of tuberculin. That it may be harmful if used incautiously seems certain. That it is a potent factor for good in selected cases of localized tuberculosis seems also certain.

HODGKIN'S DISEASE WITH EOSINOPHILIA: REPORT OF A CASE WITH AUTOPSY.

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THE presence of eosinophiles in the glands of Hodgkin's disease, or pseudo-leukemia, has been observed in a number of cases since 1892, when Goldmann first called attention to their presence. Some of these cases showed eosinophiles in other organs, but their presence in marked excess in the blood has almost never been so striking that they have been a clinical as well as a pathological factor.

The following case of Hodgkin's disease at the Worcester City Hospital, in the service of Dr. Ray W. Greene (whom I wish to thank for his permission to report the case), presented such a very unusual and marked eosinophilia, both in the blood and in several of the organs, that there exists sufficient excuse for reporting it.

Clinical history: D. S., fifteen years old, born in Worcester, Mass., of Swedish parents, entered the Worcester City Hospital on March 18, 1907.

Family history: Negative, except that his father was insane for five years, and one brother was in the hospital about the same time with osteomyelitis of the femur.

Previous history: He was always sickly, working ten hours a day for the last year.

Present illness: Before entrance he had been ill about four months, but three months before this some swellings began to appear on both sides of his neck and in his groins. These never gave him any trouble, but have been constantly present. About the second week in December, 1906, he felt tired and run down, with a backache which at that time he complained of as low down in the lumbar region. Up to two weeks before entrance he was up and about the house most of the time. Then followed one week of severe diarrhea, he having six or seven movements of the bowels a day. At the same time there developed a swelling of his face and legs, and occasional nausea and vomiting. For four months dating from November he had a cough, coming on insidiously, with expectoration. During this time he had a few attacks of dyspnea. At first he had some pain in his chest, but there was none later on. His appetite was fair, but he slept poorly.

Physical examination showed a rather poorly developed and poorly nourished boy, the skin and mucous membranes pale, marked edema of face and legs, considerable loss of subcutaneous tissue, and pupils of equal size and reacting alike. In the cervical, axillary and inguinal regions (especially in the right inguinal region) there were enlarged lymphatic glands of various sizes, from about half a centimeter to about two and a half centimeters in the longest diameter, some being in chains.

The apex of his heart was in the fifth intercostal space, about one and a half centimeters outside the nipple line. The right border was at the right edge of the sternum. No murmurs were heard.

His lungs showed dullness on percussion at both

bases, with numerous fine moist râles, and on the right side there were diminished respiratory sounds, but normal fremitus. His breathing was rapid, though not labored, both sides of the chest moving freely and apparently equally.

The liver dullness extended from the sixth rib to about three centimeters below the costal margin, giving resistance on palpation, but the lower edge was not felt.

The abdomen was full and tympanitic, except in the flanks, where it was thought that shifting dullness could be made out. The kidneys and spleen were not palpable. The knee jerks reacted equally.

Sputum examination showed no tubercle bacilli.

A blood examination showed: hemoglobin 40%, white cells 49,000, red cells 1,470,000. (These red cells were not counted directly, but were estimated by comparing the relative number of white and red cells in a hundred microscopic fields.) A differential count of 500 white cells showed:

		Absolute number per cmm.
Polymorphonuclear neutrophiles,	27.4%	13,426
Small lymphocytes,	.6%	294
Medium sized lymphocytes,	2.6%	1,274
Large lymphocytes,	.6%	294
Transitionals,	.6%	294
Eosinophiles,	68.2%	33,418
		49,000

The red cells showed considerable poikilocytosis, and some achromia. There was some, but not a general, increase in the size of the cells, some macrocytes and some microcytes. One normoblast was seen, or 98 per cubic millimeter.

A differential count of 200 white cells of the same specimen by Dr. J. B. Manning (to whom I am also indebted for the three white counts) showed:

Polymorphonuclear neutrophiles,	27%
Small lymphocytes,	3%
Eosinophiles,	70%

During this count one blast was seen.

March 19. A systolic murmur was heard at the apex and base of the heart, but only when the patient held his breath.

March 20. The chest was full of fine and medium sized and coarse râles with prolonged expiration giving rise to dyspnea. The urine was of normal color, acid reaction; albumin and sugar were absent. A differential count of 500 white blood cells showed:

Polymorphonuclear neutrophiles,		31.2%
Small lymphocytes,		2.0%
Medium sized lymphocytes,		3.2%
Large lymphocytes,		.8%
Transitionals,		1.8%
Mast cells,		.2%
Eosinophiles, polymorphonuclear (one of these showed a process resembling a pseudopod),	57.0%	60.8%
Eosinophiles showing only part of the protoplasm stained with eosine,	3.6%	
Eosinophiles, mononuclear,	.2%	

The red cells showed some variation in shape and size, and a few were seen larger than normal, but hardly to be classed as macrocytes; more were smaller than normal. A few oval forms were seen.

March 23. Condition unchanged. White count 31,000.

March 24. Examination of stool showed no parasite eggs. Some cells were seen resembling the ova of ascaris lumbricoides and oxyuris vermicularis, but as

at autopsy a careful search revealed no parasites these forms were probably vegetable cells.

March 25. There was dullness, especially marked, at the base of the right lung, with bronchial breathing and fine and medium sized moist râles. Fine and medium sized râles were scattered throughout the chest.

March 26. Examination of the blood showed: hemoglobin 35% to 40%. A differential count of 500 white cells showed:

Polymorphonuclear neutrophiles,	50.2%
Small lymphocytes,	4.0%
Medium sized lymphocytes,	.8%
Large lymphocytes,	.4%
Transitionals,	1.0%
Myelocyte (?),	.2%
Eosinophiles,	43.4%

In this count 9 normoblasts were seen (one with a divided nucleus). Besides these others were seen with two or three divisions to the nuclei, and one megaloblast. The red cells showed some variation in shape and size, an occasional macrocyte, frequent microcytes and some poikilocytosis. There was considerable achromia.

March 27. Considerable edema of lungs. Pulse gradually became weaker, and respiration more labored. The patient died at 11.15 A.M.

While he was in the hospital his temperature ranged somewhat irregularly between 100° and 102.6°, his pulse varied from 120 to 136, except on the day of admission, when it was 144, and his respirations were between 32 and 40, and on all but the first and last days were nearly uniformly 34.

The autopsy was performed March 27, 1907, four and a half hours after death.

Anatomical diagnosis: Hodgkin's disease; involve-

ment of the cervical, axillary, inguinal, mediastinal, retroperitoneal glands, and glands of the lesser curvature of stomach, involvement of the liver, spleen and lungs. Persistent thymus gland.

A well developed and poorly nourished white boy. Length, 5 ft. 3½ in. Some suggillations of the posterior surface of the body. Pupils moderately dilated. Considerable edema of face, hands, feet and legs, and a little of the trunk.

The *thymus* gland was found persistent and enlarged. It was swollen and infiltrated.

The *pericardial* cavity contained four or five ounces of clear fluid.

The *heart* weighed 200 gm. and showed no valvular changes.

Glands of above-mentioned regions were enlarged, of firm consistency and discrete. Sections of three of these, as of other organs, were mounted in paraffin, and some stained by Unna's method with methylene blue and eosin, and some stained with Wright's modification of Leischman's stain. As a rule the eosinophiles stained better with the latter, but one or two specimens, stained by Unna's method, show them best; and the sections as a whole are better when stained in this way. Specimens fixed in celloidin and stained by hematoxylin and eosin failed to show any eosinophiles for some reason, so these specimens were all passed back through alcohol and remounted in paraffin.

Sections of a bronchial lymph gland from the neighborhood of the right bronchus show a marked hyperplasia of new formed tissue. As a whole, the glandular structure is lost. While certain areas show a predominance of lymphoid cells, yet the follicular character is gone, and there is a well defined hyperplasia through-

out. The capsule is thickened, but there are no fibrous septa.

Microscopically, the gland consists of a minimum of reticulum in which are spindle and oval or epithelioid cells of various sizes, some plasma cells and giant cells containing two or three to six or eight nuclei and with pale blue protoplasm. The nuclei of the epithelioid cells occasionally show mitotic figures. There are some polymorphonuclear leucocytes and a great abundance of *eosinophiles* with granular protoplasm scattered rather evenly throughout the gland; no more numerous, however, at the periphery than in the center. These have nearly all trilobed nuclei, but occasionally one with a bilobed nucleus is seen, or a smaller cell with a small round nucleus. Certain areas contain particles of brownish pigment.

Another of the lymph glands (probably mesenteric), enlarged to about 3 cm. in length, shows a marked abundance of hyperplastic cells. The gland is divided about one third from one end by a septum of fibrous cells, while the capsule is a fairly thick fibrous structure. There are a few areas composed of lymphoid cells, also containing some polymorphonuclear leucocytes and plasma cells, a few giant cells and oval-shaped or epithelioid cells, and a few eosinophiles. Most of the gland shows, however, a diffuse hyperplasia of new formed cells in a network of fibrous tissue, which in places is quite abundant to the exclusion of other cells. These cells consist for the most part of various sized oval-shaped or epithelioid cells, generally of moderate size, of spindle cells, and frequent giant cells, usually with 3 or 4 nuclei and a pinker protoplasm than the others, but occasionally containing more nuclei sometimes arranged in a circle. There are also plasma cells and some leucocytes. The eosinophiles are not so

numerous as in the other gland or in the lung, liver or spleen, or else take the stain poorly, which seems rather to be the case. In a few places, however, they are fairly numerous. There is one area of necrosis filling about one third of the field of the low power objective (Leitz No. 3).

The left pleural cavity was normal. The *right* contained about a pint of clear fluid.

The left lung weighed 860 gm. and showed a few scattered small, firm, white areas similar to those of the right.

The right lung weighed 560 gm. and showed peculiar areas scattered throughout of white to light brown indurated tissue, especially marked at the base behind, a cross-section of this being from 5 cm. to 8 cm. in diameter. Here it was somewhat firm, with muco-pus exuding from the bronchi. This tissue also extended up along the median side near the hilus, bordering on enlarged lymphatic glands.

Microscopical sections of this area show in paraffin mounts stained both by Unna's methylene blue and eosin, and by Wright's stain, normal lung tissue which in many places is filled with cells, sometimes becoming a solid mass of abnormal tissue. These cells consist of mononuclear cells of a round and oval shape, or epithelioid cells, with nuclei both small and medium sized, and frequently vesicular, and occasionally there is a spindle cell. At times they contain vacuoles. In places the background consists of fibrous and spindle cells. Throughout this new formed tissue there are scattered some polymorphonuclear neutrophiles, lymphoid and plasma cells, and there are many *eosinophiles*, in places quite abundant. Most of them are polymorphonuclear with a trilobed nucleus, and with granular protoplasm, while others have a round or oval

nucleus at one end. These cells are in the new-formed tissue, and at times in the exudate contained in some of the bronchi, though often absent. Mitotic figures occasionally occur in the epithelioid cells. The blood vessels also contain a few eosinophiles. The alveoli and bronchioles, both those appearing normal and those whose walls are thickened and infiltrated, contain an exudate of blood, some endothelial cells, lymphoid cells, and polymorphonuclear neutrophiles, and, as above stated, at times eosinophiles. The lymphatics and capillaries are somewhat dilated. In places there is an apparent organization going on in the alveoli resembling an organizing pneumonia. This is co-ordinate with the Hodgkin's disease, but not a part of it. Some of the erythrocytes are stained pink, and others yellow. Several sections of this new-formed tissue were stained for tubercle bacilli, but none were found.

The liver was enlarged, weighing 1,700 gm. The appearance when fresh was mottled, due to the contrast of normal brown red areas against the interspersed abundant white areas of "pseudo-leukemic" tissue, which vary from the size of the head of a pin, or less, to ½ cm. in diameter. The surface was smooth and regular.

Microscopic sections stained by both Unna's and Wright's stain show the parenchyma with some cloudy swelling and considerable infiltration of the liver cells with fat, and some intercellular invasion of polymorphonuclear leucocytes. At the corners of the lobules are areas varying in size, generally round or polygonal in shape, near and surrounding the bile ducts and vessels, at times quite large, infiltrating irregularly and nearly replacing whole lobules. They correspond to the white areas of the gross. They contain connective tissue and a variety of hyperplastic cells, spindle cells,

oval or epithelioid cells and medium sized mononuclear cells with a vesicular nucleus, a few of which have a pinkish protoplasm with Wright's stain, a few lymphoid cells, plasma cells, and a considerable number of polymorphonuclear neutrophiles. There are often collections of lymphoid cells, but no large areas of these. There is an occasional small-sized giant cell with the grouping of three or four nuclei in the center, and a bluish protoplasm. The epithelioid cells are occasionally undergoing mitosis. Some areas are more fibrous, some have more spindle cells, some have more of the other varieties, some have no ducts. Throughout the tissue are numerous *eosinophiles*, quite abundant, especially in the areas of new-formed atypical tissue, but also present among and invading the parenchyma. These are similar to those heretofore described. One on careful focusing gave the appearance of thrusting out a pseudopod. The central cells of the lobules contain an excess of blood pigment. Erythrocytes are scattered throughout, some staining pink, and others yellow.

Spleen: Slightly enlarged, weighing 270 gm., of normal red color, but giving the suggestion of the porphyry appearance from minute whitish areas. One such area is about one half a centimeter in diameter, oval in shape. Trabeculæ markings were normal. The capsule was normal, and the surface smooth.

Microscopical examination of sections, stained both by Unna's and by Wright's stain, show the trabeculæ normal. In places they contain spindle cells. A few small Malpighian bodies are present, containing lymphoid cells, a few leucocytes, an occasional spindle-shaped cell of medium size, an occasional red blood corpuscle, and frequently an abundant number of *eosinophiles*. Scattered throughout are several pale-

staining areas somewhat larger than the Malpighian bodies. Sometimes these are fibrous in character, though containing a few each of the above-mentioned cells, but sometimes they are cellular, containing oval or epithelioid and spindle-shaped cells. The larger white area, mentioned above in the gross, contains a hyaline-like background, in which are scattered a few of the above-mentioned cells, excepting the eosinophiles, and a number of nuclei, especially of lymphoid cells and leucocytes. One area seems to contain chiefly these extruded nuclei.

The rest of the spleen pulp consists of a stroma infiltrated with atypical small and medium-sized, round and oval cells, with both small and vesicular nuclei which occasionally are dividing. There are also spindle cells, and an occasional giant cell with pink or bluish protoplasm and three to six nuclei. There are lymphoid cells, some polymorphonuclear leucocytes together with an abundance of eosinophiles, in places very thick. These stain somewhat better by Wright's method, though well by Unna's. These have generally a trilobed or horseshoe nucleus, often, however, small and solid, occasionally larger, and more vesicular. Rarely there is a larger form with nuclei in opposite sides, and occasionally the nucleus is protruding. Throughout are scattered erythrocytes in places in large masses, often staining a golden red color, or sometimes a yellow, while there are collections of blood pigment of a dirty yellow.

Kidneys: One weighed 140 gm.; the other 120. *Macroscopically*, the cortex was normal, and the kidney as a whole was rather pale. *Microscopically*, there is some cloudy swelling of the convoluted tubules, which as a rule contain a considerable amount of granular material. The glomerulæ show a slight increase of the

nuclei, and occasionally a slight desquamation into the periglomerular space.

The stomach, intestines and appendix were normal. The intestines contained no evidence of parasites.

The diaphragm and muscles of the chest and abdominal cavity were smooth, and macroscopically gave no evidence of the presence of trichinæ.

Unfortunately, the *bone marrow* was not examined.

The pathology of Hodgkin's disease has been fairly definitely settled since the researches of Reed were published in 1902. Whatever the relation of Hodgkin's disease to leukemia, lymphosarcoma, sarcoma of lymph glands, and tuberculosis, if there is any one pathological condition that is a type of the disease, then aside from the general eosinophilia the case now reported corresponds to that type.

Hodgkin's disease is characterized by a hyperplasia of lymphoid tissue, the cells, many of which probably originate from the reticulum, consisting of many varieties of epithelioid, spindle, lymphoid and plasma cells, eosinophiles, fibrous cells, in any lymphoid structure of the body, notably the lymph glands, liver and spleen, the latter acquiring the so-called "red-porphyry" appearance. Pinkus [1] states that the lymph glands show the normal arrangement with a proliferating center of large cells and a peripheral layer of small cells, the histological picture corresponding exactly to that of lymphatic leukemia. Other authors,[2] however, give a different and more specific pathology.

Dorothy Reed [3] says: "In the smallest gland examined . . . we found only proliferation of the flat so-called endothelial cells, which cover the reticulum of the lymph sinuses, and of the large cells of the centers of the lymph nodes which are presumably identical cells. Mitotic figures in cells of this description are frequently seen. . . . As the process advances we find the lymph spaces filled with masses of lymphocytes and proliferating endothelial cells. The presence of these newly formed cellular elements destroys the normal appearance of the gland. . . . The endothelial cells, which show many karyokinetic figures, in proliferating form large epithelioid cells with vesicular nuclei. Numerous giant cells with one or more nuclei and prominent nucleoli appear in great numbers. . . . Occasionally a very large giant cell with many small nuclei peripherally arranged is seen. . . . The lymphoid cells . . . are of the usual small type. . . . Plasma cells are often observed in almost as great numbers as the lymphocytes. Eosinophiles are usually abundant throughout the tissue spaces, except in the germinal centers of the follicles. . . . As the process advances the connective tissue shows marked proliferation. The framework of the gland becomes increased and bands of connective tissue, starting often from about the vessels gradually break up the gland substance into coarse lobules . . . at the expense of the other cells. . . . The capsule of the gland usually shows no change, except possibly some thickening."

Eosinophiles were first observed in a case of Hodgkin's disease or malignant lymphoma in the lymph glands by Goldmann [4] in 1892. Since then they have been observed by other writers,[5] and although they were thought to have a certain diagnostic value, still they are not characteristic since they are found occasionally in other varieties of lymphomata, and they are by no means constant in Hodgkin's disease.[6] In several cases of Hodgkin's disease they have been, however, very numerous.

A case of Hodgkin's disease where the eosinophiles have invaded the liver, spleen, lung and lymph glands in such large numbers and occurring in the blood to such an extent, namely, 68.2% or 33,418 per cubic millimeter in a total leucocytosis of 49,000, I have been unable to find reported. Dreschfeld,[7] in 1892, stated that eosinophiles were present in fairly large quantities in the blood in some cases, but specified no examples.

Cabot, in 1897, cited one case [8] with 9.3% eosinophiles, the white count not being increased, and in 1898 cited another [9] with 7%, or 826 eosinophiles in a leucocytosis of 11,800.

Einhorn,[10] in 1902, reported a case with 10% eosinophiles or 730 per cubic millimeter in a white count of 7,300. Later there were 12.4%. Longcope,[11] in 1903, reported a case with 2.8% eosinophiles or 563 in a leucocytosis of 20,100, in which later the percentage fell to 2.4%, but the absolute number rose to 1,872 in a white count of 78,000.

They were numerous in the glands, and increased in the bone marrow.

Longcope,[12] in 1906, reported a case showing 13.2% or 1,491 eosinophiles per cubic millimeter with a total leucocytosis of 11,300, a few large mononuclear eosinophiles in the thymus, but only a few were noted in the spleen and in the lungs; none were seen in the liver; and there was an increase of eosinophilic myelocytes in the bone marrow.

Pepper [13] has recently reported a case with 16% of eosinophiles, or 4,608 in a total white count of 28,800; enormous numbers of eosinophiles were found in an excised axillary gland. He also mentioned two other cases at the Pennsylvania Hospital, with 8.8% and 10.6%, respectively, of eosinophiles in the blood. Of twenty cases of Hodgkin's disease he found 20% had eosinophilia.

Nowack,[14] in 1905, reported a case with 24.5% eosinophiles per cubic millimeter, or 940 per cubic millimeter in a white count of 3,840.

Several other cases [15] have also been reported, showing a slight absolute increase of eosinophiles in the blood, varying from 250 or 300 per cubic millimeter (the upper limits of normal)[16] to 1,173 and up to 5% (the normal being 1% to 4%),[16] but in the organs they were numerous only in the lymph glands, except one case [17] with 4.4% eosinophiles or 550 in a white count of 12,500, with abundant eosinophiles in the lymph glands and spleen, and a few in the liver and lung.

Another case [18] showed eosinophiles in the spleen and liver, while they were numerous in the lymph glands. In the blood, however, there were only 272 per cubic millimeter. A few other cases [19] showed a few eosinophiles in the spleen or liver, but no large excess in the blood. On the other hand, in a case of lymphosarcoma colli [20] 60,000 eosinophiles per cubic millimeter have been found.

The small relative number of lymphocytes in this case (3.8%–6%) is consistent with a diagnosis of Hodgkin's disease. Notwithstanding that it has been asserted that in Hodgkin's disease there is a relative lymphocytosis,[21] this statement is disputed,[22] and there is sufficient evidence to show that in a certain proportion of cases there is a normal or low number of lymphocytes.[23] That the proliferation in the lung is not evidence of a sarcoma is supported by two cases of Hodgkin's disease reported by MacCallum,[24] in one of which the disease invaded the right lung, and in the other, both lungs. Apparently, Hodgkin's disease is a hyperplasia of pre-existing lymphoid tissue, anywhere in the body, rather than an infiltration or transplantation of new growth cells.[25] Pseudo-leukemia gastro-intestinalis, a recognized type of disease, is an example of this.[26]

The presence of dyspnea in the case under discussion possibly may be considered evidence of asthma, and as such a sufficient cause for the excessive eosinophilia. But it is not so likely that this was the cause of the eosinophilia, as

that the hyperplasia and changes in the lung were the cause of the dyspnea. Further, I am not aware that asthma causes a marked presence of eosinophiles in the various internal organs. In a pure asthma the total white count is only slightly raised, if at all, and when bronchitis is present the count runs from 6,000 up to 26,000,[27] although one case showed 45,000,[28] running up to 68,000 before death. The maximum percentage of eosinophiles in asthma reported is 53.6%,[29] but their absolute number was only 4,449 per cubic millimeter in a white count of 8,300, while another case showed 25% or 13,000, in a white count of 52,000,[30] but still considerably below the percentage and absolute number in the present case. Also our case had had no recent attack of dyspnea at the time of entrance, and it was not till two days later that there was any suggestion of an asthmatic attack, and then, instead of the percentage of eosinophiles rising, they fell from 68.2% to 60.8% with a falling white count. So the most we can say is that if there was any true asthma present in our case (which is extremely doubtful) its influence on the production of eosinophiles was only slight, partial and contributory with other causes inherent to the Hodgkin's disease.

Being of so marked a type, and differing so from the usual run of Hodgkin's disease, and unless recognized as a type so likely to lead to confusion in diagnosis, the present case is worthy of the descriptive title, *Pseudo-leukemia Eosinophilica.*

The origin of these eosinophiles is held by Opie [31] to be the bone marrow, although others maintain they are formed locally in various affections. As Longcope [32] says. in Hodgkin's disease, " We can only suppose they accumulate in the tumor nodules by one of two methods. On the one hand, it is possible that they are formed locally in the lymphomatous tumors; on the other hand, they are brought to this situation by the blood stream." Goldmann [33] and Dorothy Reed [34] held this latter view. In our own case the preponderance of eosinophiles in the blood would favor also this view. We have, in all likelihood, what is probably an exaggerated type of the frequent occurrence of eosinophiles in Hodgkin's disease, and not a blood disease *sui generis*, carried a degree further than Longcope's, Nowack's and Pepper's cases to an eosinophilia of many of the organs.

In conclusion, I wish to express my thanks for advice and assistance to Drs. Henry A. Christian, Frederick H. Baker and Ernest L. Hunt, and to Miss Ora M. Mills.

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SAHLI'S BUTYROMETRIC TEST OF GASTRIC FUNCTION.*

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IN 1902 a method of stomach examination was published by Sahli,[1] of Berne, and by Seiler,[2] his assistant, which from its ingenuity of conception and its theoretical advantages promised much. A few articles, however, soon appeared which questioned the reliability of the test, and also criticised it as too complicated for practical use; but articles dealing with the subject have been too few to lead to definite conclusions. Since the method must continue to attract attention as appearing in Sahli's valuable book upon diagnostic methods,[3] and since in its author's hands it is reported in later communications as still being used with satisfactory results, a further consideration is desirable.

In principle the test is a development from the earlier attempts, notably those of von Mering and of Strauss, to measure the activities of the stomach by introducing into it with a test diet some substance not acted upon by the stomach which in subsequent tests of the stomach contents might serve as an index of the amount of the test

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diet still remaining. Sahli's test is also performed with more stress upon quantitative determinations of amounts, given and withdrawn, than are the older tests. The following advantages are claimed for it: (1) In addition to determining the simple acidity of the mixed contents it is possible to determine the composition, by showing to what extent the specimen is composed of the substance ingested, and to what extent it is composed of gastric juice. (2) The amount and the acidity of the pure gastric juice can be determined; thus one can distinguish between hyperacidity and gastrosuccorrhea, and between subacidity with secretion normal in amount and subacidity due to diminished secretion. (3) Numerical values may be obtained indicating the degree of gastric motility; this may be of value in determining the degree of stasis in cases of pyloric stenosis and in showing variations resulting from medical or from surgical treatment. (4) All data to be obtained by means of the Ewald breakfast are said to be obtained as well by this method. (5) The process is not disagreeable to the patient. The soup employed as a test meal is not distasteful, and by reason of its fluid consistency it can be easily and rapidly withdrawn.

The theoretical basis of the test deserves careful study. The test soup, of which 300 ccm. are given, is esentially a stable fat emulsion, a sample of which is kept for comparison with what is later obtained from the stomach. The fat percentage is determined, 1st, in the original soup,

and, 2d, in the stomach contents obtained an hour after ingestion. In normal cases the fat percentage in the stomach contents is found to be only about a half as great as that of the original emulsion. Now since fat cannot be absorbed from the stomach this fall in the fat percentage must be due to *dilution* of the fluid ingested *by gastric secretion.* The relative fat percentages measure this dilution since excessive secretion obviously causes excessive dilution, and lessened secretion causes a less degree of dilution. Thus, in the contents obtained, it can be learned how much is soup and how much is secretion. The proportion of secretion in the contents thus being known and the acidity of the total contents being easily determined by the usual titration, the acidity of the pure gastric juice can be calculated. To obtain an index of motility the amount of contents is measured, and the extent to which this is composed of the original soup is calculated from its fat percentage. The relation which the amount of soup residue bears to the amount of soup ingested indicates what proportion of the test emulsion still remains in the stomach at the end of an hour, and what proportion has passed on beyond the pylorus.

The test is performed as follows: A soup is prepared by heating 15 gm. of butter and 25 gm. of flour in a pan with constant stirring until the mixture becomes browned to the color of strong coffee with milk. To this are added slowly 350 ccm. of hot water and the whole is boiled for five

minutes, after which water is added up to the original 350 ccm., and also 3.5 gm. (1%) of salt. This soup is fairly agreeable in taste and is a stable emulsion of the butter fat, without tendency to separate in layers of different concentration.

Of this soup, still hot, the patient is given 300 ccm. to be eaten with a spoon. The remaining 50 ccm. are kept for subsequent fat estimation. The patient's stomach should be washed clean before the soup is given.

After an hour the stomach contents are withdrawn as completely as possibly, and then 300 ccm. of warm water are allowed to run in and out, several times, to determine the amount of residue after the method of Matthieu,[4] as will be described later.

The stomach contents obtained should present the appearance of a perfect emulsion without visible fat globules.

Three specimens are then at hand which are, the materials for laboratory study,—the original soup, the stomach contents and the washings with the 300 ccm. of water. The ordinary chemical tests of the contents are first performed as with the contents after the Ewald breakfast. Free HCl † and total acidity are determined quantitatively. The lactic acid and the guaiac or benzidin tests or any other tests usually tried may

† Töpfer's agent is rapidly decomposed when added to this fat-containing material. In quantitating the free HCl, therefore, successive drops of Töpfer's solution on a porcelain plate, or filter paper saturated with Töpfer's solution, are touched at intervals during the titration with a glass stirring rod dipped in the contents, as the NaOH solution is run in.

be made, but are not an essential part of this method. The washings with the 300 ccm. of water are next tested for total acidity. From this we are in the position to apply the formula for estimating the amount remaining in the stomach after no more pure contents can be withdrawn through the tube:

$$\frac{x=300\times b}{a-b},$$

x being the amount of residue in centimeters; 300 ccm., the amount of wash water; b, the acidity of the washings; and a the acidity of the undiluted contents.

The result of this calculation added to the actual amount of contents is the total amount contained in the stomach at the conclusion of the test.

Thus the amount contained in the stomach being known, its composition, and the relative amounts in it of gastric secretion and of test soup are to be estimated. To this end the fat percentage of the original soup (F) and of the stomach contents (f) are determined. Sahli and Seiler recommend a modification of Gerber's butyrometric method. The author has found that the small tubes sold in this country for testing milk by the Babcock process are sufficiently accurate for purposes of the test. These are filled with 5 ccm. of the contents or of the fat emulsion, to which is added 1 ccm. of amyl alcohol and then concentrated sulphuric acid up to the shoulder of the tube. Shreds of mucus are first to be removed by forceps. Both tubes so filled are then mixed by rotation and then centrifuged for five minutes. The tubes are then allowed to stand

upright in hot water for a few minutes, after which hot water is introduced until the surface of their contents reaches the zero point of the graduations. After a second centrifugalization of one minute the results are read off. It is necessary to work rapidly to prevent cooling and contraction in the bulbs.

The reading ("f"), the percentage of fat in the stomach contents, divided by ("F"), the percentage of fat in the original soup, indicates the proportion in which the stomach contents are composed of soup ingested. In normal cases the value (f) is found to be approximately half as great as (F), showing that the contents are made up of nearly equal parts of soup ingested and of secretion. To obtain absolute amounts of soup and of secretion the amount of the total contents (including the estimated residue) is multiplied by $\frac{f}{F}$; the result is the number of cubic centimeters of the test soup remaining in the stomach at the end of the hour. The difference between this amount and the total contents is the amount of secretion. To obtain the acidity of the pure secretion the acidity of the mixed contents is multiplied by $\frac{F}{f}$. Normally, according to Seiler, this is from .35% to .44%.

The amount of test emulsion remaining in the stomach at the end of the hour being known, the difference between this and the original 300 ccm. must have passed through the pylorus to the intestines. In normal cases, it is said, the total residue should not be over 160 ccm., the amounts

of secretion and of soup residue varying between 30 ccm. and 80 ccm. The amount of the test fluid passing through the pylorus within the hour should be from 75% to 90%.

A few illustrative cases may serve to show the significance of the results obtained.

CASE I. A man aged twenty-eight, a shoe-worker, had complained for five months of poor appetite, eructations and acid regurgitation, pyrosis, pain worse an hour after meals, and occasional nausea. He was neurotic and overworked, but had not lost weight. By the method described above the following values were obtained. Total residue 65 ccm., a low amount, suggesting high motility. In this free HCl was present to .10% and the total acidity amounted to .146%. The fat percentage of the original emulsion (*F*) was found to be 1.8% and that of the stomach contents (*f*) was .8%. From this it follows that the total residue of 65 ccm. was made up of 36 ccm. of secretion and of 29 ccm. of the original soup. The acidity of the contents being .146, the acidity of the pure secretion must be .26%.‡ The soup residue of but 29 ccm. shows that over 90% of the test fluid has passed through the pylorus within an hour. These results show no notable abnormality of function but suggest the presence of a hypermotility such as is often present as a part of a gastric neurosis. (See also Case XIII in table.)

CASE XVIII. A man aged forty-three had com-

‡In this case the directions of Sahli, who uses the total acidity as the basis for his calculations of the acidity of the gastric juice, were followed. Except in earlier determinations, however, the author has based this calculation upon determinations of the total HCl by Congo red, or by the alizarin method, so as to leave out of account the slight acidity of the soup itself. The acidity values are thereby somewhat lowered, but must be nearer to the truth.

plained for ten months of distress beginning immediately after meals, with pyrosis and belching of wind, gradually increasing. For six weeks before entering the hospital he had had attacks of vomiting about once in three days, after which he would feel better for a day. The vomitus was, as a rule, large in amount, watery and sour, thought not to contain food, but containing a dark-brown sediment. The man had lost 55 lb. in six months. The fasting contents on the day after entrance were 630 ccm., slightly turbid, with slight brownish sediment, few starch granules and fat drops, free HCl .22%, total acid .24%, lactic acid absent, guaiac test positive. Daily lavage showed similar contents of the fasting stomach although the amount gradually diminished. Seventeen days after entrance the amount of fasting contents was 240 ccm. Sahli test performed on this day resulted as follows, Total residue 420 ccm.; Free HCl, .146%; total acidity, .22%; secretion, 327 ccm.; of acidity, .28%. Soup residue, 93 ccm. Per cent passed out of the stomach in an hour, 69%. The high relative amount of secretion shows strikingly the condition of hypersecretion or gastrosuccorrhea. (Absence of pyloric stricture is probable from the complete disappearance of gastric symptoms during the next year.)

Case XXI. A man aged forty-five, who for two years had complained of gradually increasing sense of fullness in the stomach, with eructations and regurgitation, showing an emaciated condition, with visible gastric peristalsis, was found by this test to have a total contents of 454 ccm., calculations from which showed that *only* 16% of the test emulsion had passed the pylorus. Operation by Dr. M. H. Richardson revealed a ring-like cancer at the pylorus which was removed by pylorectomy. Three weeks after the operation the

test was repeated and the motility coefficient was found to have risen to 44%. (Fifteen months later the patient died of typhoid fever; at autopsy the union of stomach and duodenum showed almost no sign that any operation had been performed, and no recurrence.)

Other cases examined are recorded in the appended table.

In these cases the findings have agreed well with the clinical diagnosis. In other cases among those in the table, however, and in the following cases, were found results showing considerable variations from what we should expect.

CASE XXXV. A patient with palpable cancer of the pylorus (confirmed by exploratory laparotomy), with fasting contents of 350 ccm., was found, according to the Sahli test, to have a total residue of 425 ccm., of which 340 ccm. were secretion and only 85 ccm. were remains of the soup ingested. If accuracy of the test is not questioned we must assume here a high degree of gastrosuccorrhea in addition to the symptoms of cancer.

CASE XXII gave readings still more unusual. The total residue of 135 ccm. contained the same fat percentage as that of the original soup. The patient, then in my service at the Long Island Hospital, I later found to have been at the City Hospital, and to be one of Dr. F. W. White's series of cases of achylia gastrica, yet it is to be supposed that even the small amount of saliva swallowed would give some appreciable dilution. Moreover, Koziczkowsky reports cases of apepsia

	Sahli deductions.	Clinical diagnosis.
+	Hypermotility.	Gastric neurosis.
	Subacidity. Deficient secretion.	Cancer (?)
	Slightly deficient secretion.	
	Deficient motility.	Pyloric stenosis.
	—	
	Deficient secretion. Note: Mucus present.	Gastric catarrh.
	Hypersecretion.	Gastric catarrh.
	Deficient motility.	Pyloric stenosis.
	—	Dyspepsia.
	Normal functions.	Dyspepsia.
	Anacidity.	Dyspepsia, colitis.
	—	Dyspepsia, colitis.
	Deficient motility. Deficient secretion.	Eructatio nervosa.
	Slight hypersecretion.	Nervous dyspepsia.
	Hypersecretion.	Indigestion.
	Slightly deficient motility.	Cholelithiasis.
	Slightly deficient secretion.	Dyspepsia.
	Hypermotility.	Eructatio nervosa.
	Slightly deficient secretion. Note: Mucus present.	Gastric catarrh.
	Normal functions.	Dyspepsia.
	Deficient secretion.	Dyspepsia.
	Deficient acidity.	Dyspepsia.
	Hyperacidity.	Dyspepsia.
	—	Pyloric stenosis with gastrosuccorrhea.
	Hypersecretion — high degree.	Hyperacidity.
	Hyperacidity.	Hyperacidity.
	Normal functions.	Cholelithiasis.
	—	Cancer of pylorus.
	Extremely low motility. Subacidity.	Cancer of pylorus.
	Improvement after operation.	
	Absence of secretion.	Achylia gastrica.
	Subacidity.	Gastric neurosis.
	Normal functions.	Dyspepsia.
+	Hypermotility.	Dyspepsia.
	Hypersecretion.	Hypersecretion.
	Deficient secretion, low acid. Hypomotility.	Gastroptosis.
	Deficient secretion. Hypomotility.	Gastroptosis.
	(All symptoms relieved.)	Gastroptosis.

gastrica tested by this method in which secretion was present. It was unfortunately impossible to repeat the test.

In one case only (Case XXXVI) have I obtained a result such as Koziczkowsky obtained in several cases, showing complete proof that in this case the method was at fault. The patient, a woman aged fifty-six, complaining of gas in stomach and distress after eating, relieved by belching, was found to have, one hour after ingestion of 300 ccm. of the test soup, contents containing a percentage of fat higher than that of the original soup ingested. If we exclude the possibility of absorption of water through the stomach walls, shown by Senator not to occur, this result can be explained only by the assumption that the contents in the stomach separated into two layers, the upper one becoming richer in fat and the lower one only passing through the pylorus. The emulsion of fat in the contents, however, was not broken up; unlike the contents in 8 cases excluded from this series as obviously failures of technic it contained no macroscopic fat drops. The existence of gastric stasis was excluded by the absence of residue in the fasting stomach and by the fact that dried currants given by mouth appeared normally in the dejections.

The results of other authors as to the value of this method may be summarized as follows: Koziczkowsky,[5] in Senator's clinic, made tests to determine whether the test emulsions remain homogeneously distributed in the stomach.

Drawing the contents from the stomach in two portions, the first through a tube reaching barely to the cardia and the second from the lower portion of the stomach, he found in several cases that great differences existed in the fat percentages from the two specimens. Also in a series of tests performed upon one patient his results were extremely variable. His conclusions are wholly unfavorable.

Bonniger,[6] from Riegel's clinic, speaks of the preparation of the test soup as not easy, and of the whole method as too complicated for general use. Using a different method of fat estimation, he found that in different portions of the stomach contents the fat percentages were not uniform, although the variations which he found were not so great as those reported by the last author. He also reports cases in which with the ordinary test breakfast free HCl was present, but by the Sahli test it was found to be absent. He concludes that the Sahli test soup is not a suitable substance for use as a test of acidity. He concludes that the older methods will remain the most satisfactory for general use even though Sahli's method or others on the same principle may be found useful for purposes of research.

Zweig and Calvo,[7] as a result of 52 cases tested in Gassner's clinic, accept the method as of value but with certain reservations. They find that the stomach contents are homogeneous except when the emulsion is so destroyed that the fat occurs in visible droplets, or where there are solid

particles present from faulty preparation of the material. In the presence of mucus from chronic gastritis they find the fat estimation unreliable. They find, as does Boïniger, that there is less stimulus to the secretion of acid than by the test breakfast. They, too, regard the method as too complicated for ordinary clinical purposes. In investigating cases of nervous dyspepsia, however, and in detecting conditions of atony, and especially in demonstrating hypersecretion, they consider the test of value.

Aronson,[8] working under Ewald, has used the method in 20 cases. He finds that the results in many cases were at variance with the clinical diagnoses, and has observed, without quantitative examinations, cases where the contents seemed to be not homogeneous. He considers the test too complicated for practical use and questions the reliability of the results, but still he considers that it may be of value in making diagnoses of functional disturbances and in determining the degree of acidity and amount of secretion.

Other articles have been either merely descriptive of the method or have simply given results in cases without critical discussion.

Sahli, in his book, and Seiler and Ziegler,[9] in a later article, have answered the criticisms mentioned and have suggested certain modifications which tend to overcome certain difficulties and sources of error. Seiler reports a large number of cases and continues to use the method regularly in his clinical work.

The most vital question is that as to the formation of layers of varying concentration in the stomach as described by Koziczkowsky and by Bonniger. Seiler has repeated Koziczkowsky's experiment in 32 cases and has found no great lack of homogeneity, the average difference in fat content between different layers being 0.15% to 0.25%. Koziczkowsky's poor results are attributed to faulty preparation of the emulsion, and Bonniger's to his method of fat estimation. To correct any possible influence of gravity, however, it is suggested that the patient should change his position frequently during the period of the test. It is admitted by Seiler that separation in layers might occur to a marked degree if peristalsis of the stomach were paralyzed. Koziczkowsky's variable results in the successive tests in his single case are attributed partly to faulty technic and partly to the variability of gastric functions under slight influences of environment. Bonniger's objection that secretion is not adequately stimulated is answered by Seiler's results in 28 normal cases, in which the free HCl averaged .11%, the total acidity .17%, and the acidity of the pure secretion .34%. It is suggested, however, that a raw egg be added to the test soup as an additional stimulus. The objection generally expressed that the test is too complicated is disputed. Sahli,[10] in his latest article, deals with this point at length, describing technic which obviates the need of a centrifuge.

My own observations agree in part with those of

both sides. The difficulty of technic is certainly greater than that of older methods, but I do not consider it prohibitive for use of the method in important cases. The preparation of the test soup takes about twenty minutes for a single case, and somewhat less if the roasted flour and butter (which I have kept a month in the cold without deterioration) is prepared in quantity. The chemical procedures, when the technic is once mastered, require thirty to forty-five minutes in addition to tests performed upon the ordinary stomach contents.

As to the values of free HCl in the mixed contents, it will be seen by reference to the table that among the cases in which both the Ewald test breakfast and the Sahli test soup have been used there are a few in which the free HCl after the test breakfast has been normal but in the Sahli test has been diminished or absent. In other cases, however, there has been no great discrepancy.

As to the variation in results of cases tested more than once, I am unable to express certain conviction. These variations have been considerable, but whether these variations in result indicate true variations in gastric function or misleading inaccuracies of which the method is to be accused, I cannot positively decide. It is to be noted in some of these cases how variable has been the amount of the fasting contents. It is also to be noted in these cases, as well as in Koziczkowsky's series, that one of the most variable factors has been the amount of contents at the end of the

hour. This variation obviously cannot be brought forward as evidence against the method.

I have unfortunately few cases where tests were repeated without change of conditions. Case III, from Aug. 5 to Sept. 22, presents the development of a pyloric stenosis. Case XXI, between Aug. 23 and Sept. 18, had undergone pylorectomy. In cases XXXVII and XXXVIII, although conditions seemed the same on the different days, still great variations occurred in the amounts of fasting contents and of contents at the end of the test.

It must be understood that the method, like many clinical methods, cannot lay claim to such accuracy as is required by the analytical chemist. I freely admit that the error in my fat determinations may be 0.1% in either direction, perhaps sometimes even 0.2%, which is enough to influence considerably the calculated results. Yet I feel that in cases such as Case XXXVIII the three results, roughly similar, it is true, but yet widely different, are to be explained largely by irregular action of the stomach.

Finally, as to the question of the homogeneity of the stomach contents, the question according to the decision of which the test must stand or fall: In one case (Case XXXVI), perhaps also in another (Case XXII), we have evidence agreeing with that of Koziczkowsky and of Bonniger, that separation of fat from its suspending fluid has occurred. Case XXXV may also be suspected of showing a similar process by which the fat containing portion has been the first to pass out of the stomach. I am also able to agree with Zweig

and Calvo that in certain cases, in spite of every precaution, the emulsion of fat may be broken up in the stomach so that the fat is found floating in large drops at the surface of the stomach contents. Such conditions obviously show that in these cases the test has failed. Yet I can also prove that this method is not always open to such objections. In Case XXXVIII, on Feb. 16, the contents were drawn by Koziczkowsky's method from two levels. In the first, the upper layer, the readings were as follows: (1) 1.0%, (2) 0.9+%. In the second layer (the larger) the readings were: (1) 0.8+%, (2) 0.9%. On Feb. 19 the contents were withdrawn in three layers which contained the following percentages: 1st layer, 1.1%, 2d layer, 1.2%, 3d layer, 1.0%. In testing a few of my earlier cases, observations as to this same question were made. Although I have unfortunately mislaid the readings they showed no such great variations as those of Koziczkowsky and Bonniger. Moreover, if the glaring errors found by Koziczkowsky are of frequent occurrence, it is strange that more inconsistencies have not become evident in the course of the series of cases recorded in my table.

The question naturally arises, how we are to distinguish cases in which the results are reliable from those in which they are fallacious. Sahli has answered this by advising that in every case the contents be withdrawn in two portions so as to detect undue variation. This adds to the time required by the test, but I feel that it is the only solution of the difficulty possible if we are to con-

tinue to use this test fluid which we must admit is liable in some cases to separation.

Thus we have in this method a procedure which, in spite of a liability in some cases to complete failure, offers in other cases, at the price of an hour's extra work, information, probably at least roughly accurate, of a nature which we cannot otherwise obtain. It must be admitted that the method lacks much of being an ideal application of the theoretical considerations upon which it is based. It is strongly to be hoped that better solutions of the problem which this method attempts may be brought forth.

But the final question to be considered is whether this method as it stands is to be accepted with its limitations or whether it is to be entirely discarded. Personally I feel that for certain cases, especially where there is question of impaired motility or of hypersecretion, and where circumstances demand that every effort shall be made to arrive at a diagnosis, this method is not without value.

In conclusion I beg leave to express my gratitude to Dr. Maurice H. Richardson and to the physicians of the Massachusetts General Hospital for clinical opportunities, without which this work could not have been done.

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ON THE OCCURRENCE OF STEATORRHEA UNASSOCIATED WITH JAUNDICE OR DEMONSTRABLE PANCREATIC DISEASE.

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CONFLICTING views are still held in regard to the significance of fatty stools in the diagnosis of pancreatic disease. Friedrich Müller[1] in his studies on icterus showed that the ordinary clay-colored stool of jaundice was composed largely of fat. In the three cases of pancreatic disease that he investigated fatty stools did not occur. He maintained that in pancreatic disease there was a deficiency in the splitting of the fat which would lead to a decrease of the fatty acids and soap with an increased percentage of neutral fat. Recent observations, especially those of Brugsch,[2] indicate that marked splitting of the fat may occur even when the pancreatic juice does not enter the intestine. Deuscher,[3] Zoja[4] and Brugsch believe, however, that the determination of the composition of fecal fat is of diagnostic importance in suspected pancreatic disease.

[1] Zeitschr. für klin. Med., 1887, xii, p. 45.
[2] *Ibid.*, 1906, lviii, Heft 5 u. 6.
[3] Correspondenzbl. für Schw. Aerzte, 1898, xxviii, p. 321.
[4] Morgagni, 1899. Referat im Centralbl. für inn. Med., 1899, 1.

Deuscher's careful analyses indicate that a high percentage of fatty acids occurs in pancreatic disease, and he holds that this increase is due to a lack of soap formation rather than to increased splitting of the neutral fat. The views of Zoja and Deuscher are practically in accord although one lays stress upon the diminished percentage of soap and the other on the increased percentage of fatty acids. Recent investigators have clearly demonstrated that true steatorrhea does occur in pancreatic disease unassociated with icterus.

The exclusion of bile from the intestine produces a greater relative increase in the amount of fat in the feces than does the loss of pancreatic secretion. The highest percentage of fat occurs when there is complete obstruction to the flow, both of bile and pancreatic juice.

With the co-operation of Professor Fitz one of us began several years ago a study of the composition of fecal fats in cases of suspected pancreatic disease occurring at the Massachusetts General Hospital.

Clay-colored or grayish-white stools occur under three conditions: (1) when no bile enters the intestine; (2) when the hydrobilirubin which gives the normal color to the stools is reduced to the colorless derivative, leukohydrobilirubin; and (3) the presence of a large amount of fat may obscure the hydrobilirubin and give rise to a colorless stool. Some examples of the last two conditions are found reported in the literature under the title "acholic stools without icterus."

This is a misnomer, however, because in both conditions derivatives of bile do occur in stools. It is possible that the few cases reported as acholic stools due to leukohydrobilirubin are really due to an excess of fat in the feces. No case can be accepted as belonging in class two unless it be shown that the percentage of fat in the stools is not increased. If it is increased one is not justified in assuming that the clay-colored stool is due to leukohydrobilirubin. It was at first thought that the two cases with clay-colored stools reported in this paper were due to the presence of colorless leukohydrobilirubin. Chemical analysis showed, however, a high percentage of fat.

Stools very rich in fat have been observed rarely in extensive amyloid disease of the intestine, in tuberculous peritonitis, and in tuberculosis of the mesenteric lymph nodes. The condition to be described in this paper is a fatty diarrhea without jaundice and unassociated with any demonstrable organic disease of the pancreas, intestine, or lymphatics.

CASE I. B. D., age thirty-three years, entered the Massachusetts General Hospital on Dr. Fitz's service on Oct. 30, 1903.

Anamnesis. Family history unimportant. Aside from the ordinary diseases of childhood he was always well until the onset of present trouble. Never jaundiced.

For many years he has had recurrent attacks of pain over the stomach and intestine, lasting two or three

hours usually and followed by diarrhea for a day or two. Eructations of gas were marked during these seizures. Diarrhea since the summer of 1902. Frequently has seven to twelve stools a day; rarely less than six. Bowels often distended with gas; passes much gas by rectum. Stopped eating meat in September, 1903, as he thought this caused the attacks of abdominal pain. Vomiting has been frequent. The stools have been light colored for a long time. Never noticed blood or mucus in stools. Considerable loss of weight in past year and a half. Has been able to do very little work for past year owing to general debility.

Status praesens. Fairly well developed, rather poorly nourished. Slight pallor of skin and mucous membranes. Lungs hyper-resonant. Cardiac outline normal. Soft systolic murmur over pulmonic area. Pulse regular and slow. Blood tension 125 mm. Abdomen distended. Umbilicus almost even with abdominal wall. Slight peristaltic movement visible at times. On palpation much gurgling, no masses or tenderness. Liver and spleen not enlarged. Knee kicks and plantar reflex normal.

Urine free from albumin and sugar. Bile absent. Sediment shows no casts.

Oct. 31. Hemoglobin 60% (Tallqvist), leucocytes 8,800, erythrocytes 4,096,000.

Nov. 2. Stool, consistency of pea soup. Reaction faintly alkaline. It contains a large amount of tenacious mucus. Few striated muscle fibers. Few fat droplets.

Rest in bed and a farinaceous diet improved his condition, and when he left the hospital, Nov. 20, he was having only one movement a day.

He re-entered the hospital Dec. 18, complaining again of diarrhea.

Dec. 17. Diet yesterday:

Breakfast: Cream toast, cup of cocoa.
Dinner: Boiled milk; French bread.
Supper: Boiled milk; French bread.

Specimen passed at 11 A.M. Examined at 12 M. It consists of about 75 ccm. of homogeneous, soft, clay-colored, bulky feces, without odor. Upon treating a small portion with ether the light-gray color becomes somewhat brownish. Test for bilirubin by Gmelin's method positive. Microscopic examination: Numerous sheaves of crystals (fatty acids?). No small "soap crystals" seen nor epithelial or pus cells. Much granular material. Stain for tubercle bacilli negative.

The stools continued to be clay colored until his discharge on Jan. 9, 1904. He was re-admitted Feb. 11, 1904. No loss of weight in past month. About six movements daily since he left the ward a month ago. They are sometimes clay colored and sometimes light yellow.

Feb. 19. Test breakfast: No free HCl. Total acidity 4. Two of Sahli's glutoid capsules given.

Urine voided at the end of 7 hours positive.
Urine voided at the end of 9 hours positive.
Urine voided at the end of 25 hours positive.

Feb. 21. Stools since last entrance into hospital have been straw-yellow in color. He has averaged four to five liquid stools daily. No fat crystals now found on microscopical examination.

Feb. 22. Test breakfast. No free HCl. Two of Sahli's glutoid capsules given with the breakfast at 8 A.M.

Tested for Salicylic Acid.

9 A.M.	Fluid from stomach,	1	hour	negative.
10 A.M.	Urine,	2	,,	negative.
12 M.	,,	4	,,	positive.
2 P.M.	,,	6	,,	positive.
4 P.M.	,,	8	,,	positive.
6 P.M.	,,	10	,,	positive.

Feb. 25. Test breakfast. Reaction neutral. Pepsin and rennin present. Schmidt's test for bile in stool positive.

Feb. 28. Discharged. Diarrhea less marked during last few days. Still some epigastric distention.

Analysis of Stool Passed Dec. 18, 1903.

	Composition of fecal fat.
Nitrogen, 3.3%	Neutral fat, 11%
Fat, 62.7%	Fatty acids, 23%
	Soaps, 66%

Case II. W. S., age, forty-eight years. Single, born in New York. Overseer of orange plantation in Porto Rico for the past fifteen years. Entered Dr. Fitz's service, Massachusetts General Hospital Nov. 1, 1905.

F. H. Father living and well. Mother, one brother, and an aunt died of consumption. One sister living who has consumption.

P. H. Mumps in childhood. Intermittent fever in 1890, followed three months later by "typhoid malaria." Malarial fever in 1894. Denies lues.

Habits: Tea and coffee in moderation. No alcohol or tobacco.

P. I. For the last two years he has felt "run down" and has been unable to do as much work as formerly and gets easily fatigued. For the last year has occasionally had loose movements of the bowels for a few days at a time, but in the intervals stools have been formed and have averaged one a day. Two months ago he began to have diarrhea which has persisted ever since. The movements are of the consistency of paste, sometimes watery, never formed; frequency, two to three a day. Color light yellow. Patient says they frequently contain mucus, but never any blood. They sometimes have foul odor, but as a rule the odor has not been re-

markable. Slight abdominal pain on defecation, but aside from this he has no pain. Appetite poor. Has vomited twice in the last month, once after taking porter, once after chocolate. Noticed nothing remarkable about the vomitus. Has lost flesh. Usual weight 125 lb., now 115 lb. Has never been jaundiced. No cough, dyspnea, or urinary symptoms. He left his work in Porto Rico two weeks ago, coming directly to Boston.

P. E. Well developed. Poorly nourished. Skin sallow. Over buttocks and inner aspect of thighs is an area of dark-brown pigmentation, which shows a tendency to scale, especially in the central portion. Conjunctivæ normal. Teeth poor. Throat negative. A few glands in groins, axillæ and neck the size of a pea. Lungs: Slight dullness in left supraclavicular fossa, and dullness at left base behind. Heart: Area of cardiac dullness not enlarged. Action regular and of good quality. Abdomen: Level, soft, tympanitic. No shifting dullness. No masses or tenderness. Liver: Upper limit of dullness in right mammillary line at fourth rib, flatness fifth rib. Lower border at costal margin; edge not felt. Spleen enlarged to percussion; edge not felt. Genitals normal. No edema of extremities. Knee jerks present and equal. Rectal examination negative. Prostate of normal size. No masses or tenderness. Temperature, pulse and respiration normal at entrance and remained so throughout entire stay in hospital of fourteen weeks. Weight, 102 lb. on Nov. 6. At time of discharge weight had fallen to 97 lb.

Blood: Hemoglobin 80%; leucocytes 4,800; erythrocytes 3,500,000. Stained specimen showed only a relative increase in polynuclear neutrophiles (82%).

Urine: Faint trace of albumin found repeatedly,

but never any casts. Bile was present at first examination, but not afterward.

Stool: light clay color, semisolid, no froth or mucus, odor not abnormal. Microscopical examination: No blood, pus, amebæ, or parasites. Rare ovum of Tricocephalus dispar. Guaiac test for blood negative. No tubercle bacilli present.

Patient remained under observation for fourteen weeks during which time his symptoms varied but little. Lassitude, weakness, anorexia and diarrhea were the chief complaints, occasionally nausea, rarely vomiting. The abdomen was frequently distended by gas. Pain was either absent or slight and occurred chiefly in association with abdominal distention. Movements varied from one to ten daily. The number was little influenced by treatment. Average number of stools two to four daily. Pancreatin was given without effect. The stools were examined daily. They were always bulky, semisolid, never formed, light yellow or clay colored, often noticeably frothy and of normal odor. The most constant microscopic finding was large quantities of fat occurring as drops and crystals. At times stools were seen which showed yellow streaks of practically pure fat. Muscle fibers were frequently seen, but not in large numbers and not constantly. A diet poor in meat was given. No mucus, except in December, when he was having six to ten movements daily. Occasionally the guaiac test for blood was positive; no blood was ever seen macroscopically or microscopically. The eggs of Tricocephalus dispar were sometimes found. For several days during December sarcinæ were present in large numbers. Starch granules were found in some stools. Discharged Feb. 6, 1906, slightly relieved.

Subsequent history: On leaving the hospital on Feb. 6 patient went to Syracuse, N. Y., where he

gained 4 lb. in five days. On Feb. 11, while at dinner table he suddenly vomited blood, and later in the day again vomited and also passed blood by rectum. On Feb. 13, again had hemorrhages from stomach and bowels, and on Feb. 14, further hemorrhage from bowels. At the date of writing (March 7, 1906), there was no pain and he was steadily improving. Diarrhea had ceased and he was having one formed movement a day.

Analysis of Clay Colored Stool.

	Composition of fecal fat.
Nitrogen, 3.2%	Neutral fat, 24.3%
Fat, 53%	Fatty acids, 19.1%
	Soaps, 56.6%

Commentary.—The most interesting feature in these two cases of chronic diarrhea is the fatty character of the stools. In Case I, 62.7% of the dried stool was composed of fat, and in Case II, 53%. Normally the stools contain less than 30% of fat, except in rare instances with a diet unusually rich in fat. In pancreatic disease without icterus the percentage of fat, as Brugsch has pointed out, is rarely more than 55%. As the stools were bulky and numerous in both our cases the total amount of fat not utilized by the body must have been large.

In the following table the results of our analyses of the fecal fats and those obtained in health are compared:

	Percentage of fat in dried stool.	Neutral fat.	Fatty acids.	Soaps.
Health, milk diet,[5]	21	27.8	51.3	20.9
,, ,, ,,[5]		20.5	39.8	40.5
,, bread and milk,[5]		24.8	25.3	49.7
Case I. B. D.,	62.7	11	23	66
Case II. W. D. S.,	53.0	24.3	19.1	56.6

[5] Müller: Zeitschr. für klin. Med., 1887, xii, p. 45.

It will be seen from this table that in our two cases the proportions of neutral fat, fatty acids and soaps correspond closely to those obtained in health. In the stool from Case I there was more splitting of the fat than is usual even in health. The analyses do not indicate any lessening of pancreatic digestion.

Aside from the fact that the stools are fatty there is no evidence in these cases that the disease is pancreatic in origin. A. Schmidt has recently described under the term "pancreatic achylia," cases that bear a superficial clinical resemblance to the two here reported. His patients suffered from diarrhea of long standing. There was considerable distention of the abdomen at times. The stools were frothy and contained considerable fat. Microscopic examination showed that the fat occurred chiefly in the form of droplets (neutral fat). The stools showed considerable starch. Sahli's glutoid test of pancreatic function was negative in one of his cases while it was positive in one of ours, thus supporting the view that the form of fatty diarrhea he was studying was of pancreatic origin, while the disturbance in the absorption of the fat in our cases was not of pancreatic origin. Unfortunately, Schmidt made no chemical analysis of the composition of the fecal fat so that the proportion of split fat is unknown. The nucleus or meat bag test of pancreatic disease which Schmidt has devised was negative in his cases. It is to be regretted that this test was not used by us. The percentage of fat was larger in our cases than in those of

Schmidt. He obtained 40.6% of fat in one case, and 40.1% in another. As stated in the early part of this paper, fatty stools have been studied in a few cases of severe tuberculosis of the intestine and mesenteric lymph nodes. There was no evidence of tuberculosis in our cases. In both the feces were examined for tubercle bacilli with a negative result. Weintraud[6] believes that the loss of nitrogen in the stools is less in organic diseases of the intestine than in occlusion of the pancreatic ducts. In our cases the percentage of nitrogen was within normal limits. Oppler[7] and Einhorn[8] showed that diarrhea may occur as the result of achylia gastrica. The intestinal function in these cases becomes secondarily deranged. In the absence of gastric juices connective tissue is not digested and may have an irritating action in its passage through the intestine. Our first patient had voluntarily given up the use of meat as he had noticed that it aggravated his symptoms. Repeated examinations of the gastric contents always showed absence of hydrochloric acid after the test breakfast. The study of these two cases seems to show that severe fatty diarrhea may occur in the absence of pancreatic disease and of jaundice as a result of functional or catarrhal disease of the intestine. It is not improbable that the intestinal disease, at least in the first case, was secondary to achylia gastrica.

[6] Die Heilkunde, Heft 2, p. 67.
[7] Deut. med. Wochenschr., 1896, no. 32.
[8] Arch. für Verdauungskr., i, 1895, p. 158, and iii, 1898, p. 139.

FACT AND SPECULATION CONCERNING THE NATURE OF TYPHOID FEVER.

BY MARK WYMAN RICHARDSON, M.D., BOSTON,
Medical House Pupil, Massachusetts General Hospital, 1895.

DURING the past eleven years my medical interests have centered largely in a study of immunity in bacterial disease. More especially my attention has been fixed upon one disease, namely, typhoid fever.

What is the essential nature of typhoid fever? It is an intoxication produced during the struggle between the typhoid bacillus on the one hand, and the body cells and juices on the other. The typhoid poison is a so-called endotoxin, i. e., it is contained within the body of the bacterial cell. The typhoid bacillus does not, as far as is known, produce a soluble poison and is, in this respect, fundamentally different from the organisms of diphtheria and tetanus. We do not, therefore, in typhoid, get, as a result of infection, an antitoxic immunity, in a strict sense, but one directed against the bacillus itself. In the more recent literature, to be sure, one begins to read of anti-endotoxins, and it seems probable that antibodies of this type can be developed up to a certain point. Compared with true antitoxins, however, their strength is small, and, for the purposes of this discussion, they may be disregarded. Accord-

ing to this view, therefore, there can be in typhoid no intoxication until there is a bacillary destruction. Where does the destruction take place? In the circulation, or in the tissues in intimate relation with the blood or lymph. In this connection the gastro-intestinal tract, including gall bladder, as well as the urinary bladder, ureter and pelvis of the kidney, are not to be considered as within the body. They are really outside.

How does infection take place? In the vast majority of instances through the intestinal tract. Mere presence of the organism in the intestine does not mean necessarily infection, however. Of many individuals exposed only a few become infected. The intestinal contents may harbor many typhoid bacilli, and yet the host may remain well. If the bacillus gains access to the "real body," what happens? It may be killed immediately by the bactericidal substances in the blood. It may circulate undestroyed in the blood and finally be eliminated in the bile. In the first instance, if there were only a few bacilli, the destroyed germs would not produce enough toxin to produce symptoms. In the second instance, however, the still living germ, being now in a suitable medium, might multiply rapidly in the bile and finally produce a cholecystitis. Is not this a probable explanation of those rare cases in which a typhoid cholecystitis with or without gallstones is found without any previous history of typhoid fever?

The better to picture to myself the interrelation

of these different factors of infection and immunity, I have been accustomed to compare their interaction to that of sulphuric acid upon zinc with the resulting evolution of hydrogen gas. In such a comparison the destructive immune substances correspond to the sulphuric acid, the bacilli with their contained endotoxins to the zinc; the released endotoxin to the hydrogen gas and the body to a gas receiver. A stop-cock in the gas bag, which allows a constant escape of a small amount of gas, typifies whatever power the body may have for the elimination of toxins through feces, urine, skin, respiration, etc. If now we follow out the parallel in a series of cuts we get quite a concrete picture of what the typhoid process probably is. In Figure 1 is represented the condition of health with its greater or smaller amount of natural immunity or resistance (H_2SO_4). There is no infection, no bacilli to be destroyed (Zn), hence there is no production of poison (H). The gas bag remains flat.

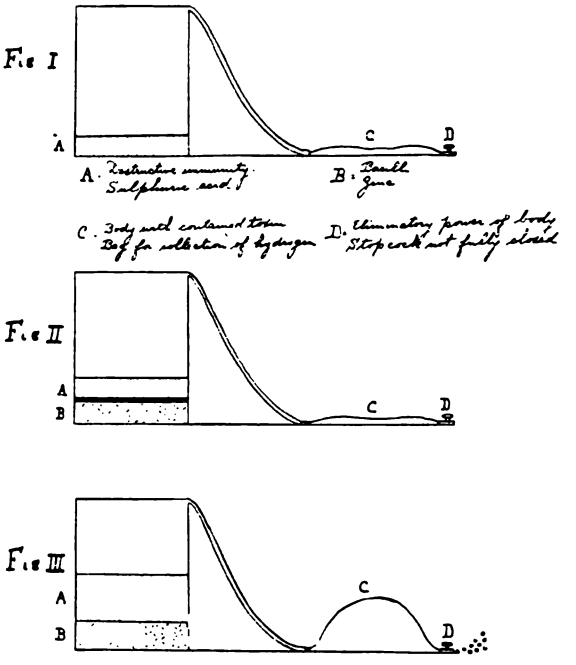
Suppose now that the bacillus enters the circulation and is neither destroyed nor eliminated, but continues to multiply. What happens? The immediate effect may be *nil*, for according to our theory there is no intoxication until there is bacillary destruction. It is, therefore, conceivable that the body should contain bacilli in large numbers and still show no signs of disease. This condition is represented in Figure 2. The acid and the zinc are separated by a glass plate, i. e.,

the destructive agencies do not for some reason act upon the bacilli. There is, therefore, no gas (toxin) production. The individual remains well. The truth of this assumption has been shown recently by the cultivation of bacilli from the blood of individuals who had been exposed to the disease, but had as yet shown no signs. This has been spoken of as a " latent " development of the bacilli, and goes on very probably for several days previous to the occurrence of a relapse as well as at the beginning of the disease.

If now we suppose that the multiplication of bacilli has been going on without symptoms, the future course of the disease will depend, first, upon the extent of this multiplication, and, secondly, upon the vigor with which the body, once aroused, attacks the invading organism. If the number of bacilli is small and the destructive agencies, once aroused, act firmly and sharply, we shall have as a result a short intoxication of marked intensity. (See Fig. 3.) With the same number of bacilli and a less concentrated attack from the forces of immunity the disease would be milder but longer. (See Fig. 4.) In case the number of bacilli was very large and the attack upon them was very sharp, or, if the multiplication of the bacilli more than kept pace with the growth of the immunity, then the increasing destruction with its resultant increasing intoxication would soon reach a point at which life would be no longer possible.

Indeed, given a body already invaded by a

large number of typhoid bacilli, a rapidly increasing and energetically acting immunity might be actually inimical to its own proper purpose, and destructive to life, because it set free too much intracellular poison within too short a space



of time. In fact this has seemed to me a probable explanation of the fulminating type of typhoid, and, possibly, of other bacterial diseases. The immunizing apparatus once aroused, acts *too* well for the good of the individual. The powers of

elimination, through skin, lungs, urine and feces, are limited, and excessive toxin production means rapid accumulation within the body. (See Fig. 5.) If, however, with the same power of elimination, this toxin production be spread out, let us say, over a period of three weeks instead of one, then the toxic condition will be comparatively mild and not dangerous, perhaps, to life. Finally in Figure 6 we have pictured the bodily condition after the disease process is over. There is, then, a large store of specific acquired immunity, sufficient, except in rare instances, to prevent any reinfection.

These points have an important bearing on the question of specific therapy, for, in the absence of a true antitoxin for the typhoid poison, we have been more and more tempted to introduce into the diseased body substances which should stimulate an increased destruction of the bacilli. This procedure is justified in cases not already very severely poisoned. In the cases, however, already hyper-intoxicated, the indication may well be, not to increase the rate of destruction of the bacilli, but, if possible, in some way, to hold it up. The blood serum of persons who die of typhoid is strongly protective in animal experiment. The opsonic index of persons moribund with the disease, I have found to be high. They do not die, apparently, because of a lack of protective substances. Do they not, some of them at least, die because their destructive power, as evidenced by their blood condition is *too* high?

In the treatment of a series of cases with the non-toxic residue of the typhoid bacillus as prepared by Professor Vaughan of Ann Arbor,[1] it seemed to me that the cases were longer but milder than the ordinary run of cases. If this was true, was

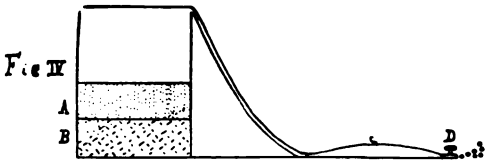


Fig. V

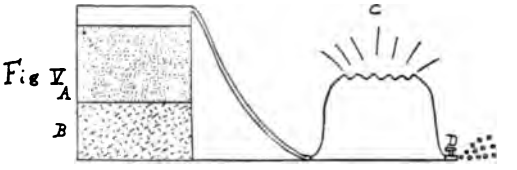
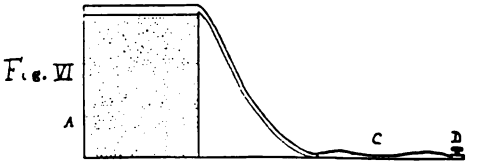


Fig. VI



it not due to the fact that this non-toxic residue of the typhoid germ, with its specific affinity for typhoid antibodies, diverted the destructive substances from the living, toxin-laden bacilli,

[1] On the treatment of typhoid fever with specific sera, filtrates and residues (Vaughan). BOSTON MED. AND SURG. JOUR., Oct. 3, 1907.

and thus made the process longer but less severe? Furthermore, cannot this idea be used as a possible explanation of the beneficial effects of cold baths in typhoid fever? The destruction of the invading germ, whether it be through bacteriolysis or phagocytosis, is accomplished largely through digestive ferments, whose action becomes much impaired in the presence of low temperatures. The cold bath, then, inhibits the action of the destructive ferments over the large expanse of skin, and toxin production is thus decreased. The temperature drops, the patient feels better, and the tissues have a few hours' respite from hyper-intoxication.

For the same reason the exhibition of drugs calculated to lower cellular activity might well be indicated. Quinine is such a drug. Its use in large doses in pneumonia has been recommended and might be justified by this reasoning.

As long as there is bacillary destruction, so long will there be evidence of intoxication. It is said that bacilli have been cultivated from the blood a certain time after the cessation of symptoms. This phenomenon must be rare, but goes to prove my contention, that the typhoid organism causes little trouble till it is dead and disintegrated.

This picture of the essential nature of the disease makes a number of phenomena observed in typhoid fever more readily comprehensible. Take, for instance, the chill, which, though in general rare, in individual cases may be very

common. According to my theory this represents a *sudden* destruction of bacilli as contrasted with the more evenly distributed production of toxin seen under ordinary circumstances. Thus the cases with sudden onset are apt to begin with a chill, their course is commonly unusually severe and their mortality is high. As stated above, it seems very probable that, in these instances, the protective substances act *too* well, and the individual is overwhelmed with toxin as a result of his excessive zeal in destruction.

In the treatment of typhoid patients with filtrates of living bouillon cultures (*loc. cit.*), chills were very common, and due, in my opinion, to sudden stimulation of the protective apparatus. Following the chill there occurred frequently a marked fall in temperature. This, to my mind, means that a period of over-stimulation was followed by a resting stage, and that, in the absence of toxin production, the temperature had to fall.

The same explanation would hold for those curious drops in temperature which, with no apparent cause, occur in typhoid fever, under routine forms of treatment. The intercurrent relapse may represent not a variation in the intensity of the infection, but a variation of the powers of resistance. Indeed, in the cases of true relapse, it is very possible that during the afebrile period, the bacilli are still there, perhaps increasing in numbers in the absence of resistance. Only when the body takes up again the work of

destruction do symptoms appear. The fact that many cases which relapse retain their enlarged spleen would bear out further the idea that bacilli have persisted.

Further, I think the characteristic temperature curve of typhoid is susceptible of explanation by the use of our theory. In the beginning we have the step-like rise in the fever, inasmuch as more endotoxin is set free than can be eliminated. It collects, therefore, in the body, the degree of intoxication receding slightly each morning only to go still higher as the result of that day's destructive activities. Having reached a high level, the intoxication is so intense that the comparatively small amount excreted has no appreciable effect upon the general condition. In the later weeks, however, when there are comparatively few bacilli in the body, then, although the daily toxin production is sufficient to carry the temperature up to a high figure, the degree of intoxication is really small, and is more than counterbalanced by the toxin excretion. Receding morning temperatures necessarily follow.

SUMMARY.

Typhoid fever is essentially a septicemia. Mere blood invasion, however, does not produce evidence of disease. Intoxication occurs mainly through the destruction of the bacilli by the body cells and fluids. Intracellular poisons are thereby

set free, and the individual then first shows signs of disease.

The intensity of the intoxication will depend upon the rate of destruction, modified, of course, by varying efficiency in elimination.

Rapid destruction of a few bacilli will cause a short, sharp attack of fever, ending perhaps by crisis.

Rapid destruction of a large number of bacilli will cause intense intoxication of longer duration. This produces the fulminating type of the disease and is frequently fatal.

Slow destruction of moderate numbers of bacilli will cause moderate intoxication of longer duration — the true " slow " fever.

If the gradually increasing immunity does not, within a reasonable time, check the growth of the bacilli, then the intoxication must gradually increase and the individual finally die.

As regards specific therapy in typhoid fever: In the absence of a true antitoxin we have had to fall back on the use of various bacterial products which have had for their aim the stimulation of the individual to destroy the invading bacilli with greater intensity.

Such treatment is suitable for those cases only which are not already hyper-intoxicated. In the presence of severe typhoid poisoning the indication may be to *check* in some way bacillary destruction. This might be accomplished (*a*) by inoculation of the nontoxic typhoid substances to divert destructive agents from the

living toxin-bearing bacilli, or (*b*) by cold baths, to combat, by low temperature, rapid phagocytosis and bacteriolysis, or (*c*) by giving drugs which shall lower metabolic activity (quinine, etc.).

PRIMARY SARCOMA OF THE PLEURA.

BY WILLIAM B. ROBBINS, M.D., BOSTON,
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(From the Laboratory of the Department of the Theory and Practice of Physic, Harvard University.)

THE following case is of interest on account of the great rarity of sarcoma primary in the pleura. The history of the case is unattainable other than that there was a tumor removed from the thyroid region at an earlier date, which proved to be a benign adenoma, and that for some time before this there were signs of fluid in the left chest with increasing dyspnea, for which the woman came to the hospital. The autopsy * showed the following:

Body of a large, well-developed, well-nourished woman. Diaphragm, right side to a height of fifth rib, on the left side to seventh rib. On the left side the diaphragm bulges down as compared with the normal dome shape.

Pleural cavities: Right pleural cavity is free from fluid. Pleura is smooth and glistening. Left pleural cavity is distended with a large amount of clear straw-colored fluid. This could not be measured but exceeded several liters. The entire pleural cavity on the left side is lined with a grayish layer, nowhere smooth, though its surface is very glistening. In general, the surface is coarsely granular and in places

* The autopsy was made by Dr. Henry A. Christian.

thrown into coxcomblike folds, some several centimeters in length. This is more marked in that portion of the pleura lying in apposition with the pericardium. This tissue is firm and on section is seen to be on the average 3 mm. in thickness, and overlies a considerable layer of fat tissue. In this fat tissue adjacent to the mediastinum there are present a few lymph nodes grayish in color from 1 to 1½ ccm. in greatest diameter. Pleural cavity on the left side extends well to the median line and consequently part of the inner surface of the sternum is lined by this above-described tissue. The lung itself is greatly compressed and lies as a flattened mass along the spinal column. Pericardial cavity free from fluid and normal in appearance. Heart is of normal size, myocardium dark red in color; valves are normal. Coronary arteries show a moderate degree of thickening and in one there is a small calcified plaque.

Lungs: Right lung is voluminous; its surface is smooth; has the usual carbon marking. Scattered over its surface are a few small, firm, slightly projecting, rounded, grayish white areas. Section of these shows them to be small grayish white masses of solid, firm, though not hard, tissue. From the cut surface of the lung exudes a large amount of frothy fluid. Portions of the cut surface are gray, other portions grayish-red in color. There are a few scattered whitish nodules as described on the surface, none exceeding 5 mm. in diameter. The bronchi contain a small amount of muco-purulent material; the mucous membrane is slightly congested.

The left lung: The left lung is compressed into a flabby, wrinkled, solid mass. Its pleura is slightly thickened and presents an appearance similar to that described for the parietal pleura, though the process on the visceral pleura is not so marked. The lung is air-

less. Its cut surface is gray or yellow-gray in color. Scattered through it, particularly along the lower posterior border, and extending from there up to the point of the entrance of the bronchi and larger vessels, there are irregular masses of firmer tissue, in general grayish or pinkish-gray in color, not sharply circumscribed from surrounding lung tissue. Elsewhere in the lungs there are a few small grayish nodules. Near the root of the lung there is an irregular cavity containing grayish-yellow puriform material, smears from which show cells of varying size and shape, some with mitotic figures. Some of these cells are well preserved, others necrotic. One lymph node in this region is of a cheesy consistence and a yellow color, like that of a hard-boiled egg. The bronchi on this side are similar to those on the right.

Abdomen: Stomach, intestines and pancreas normal. Spleen is slightly enlarged, purplish in color with smooth surface. Cut surface is dark red; Malpighian bodies are visible as grayish areas 1 to 2 mm. in diameter. From the cut surface a small amount of pulp can be easily scraped away.

Liver of normal size. Surface is smooth. Visible on the surface are a few small white or grayish areas, scarcely at all elevated above surrounding tissue. The largest of these lie in the superior surface of the left lobe and measure one cubic centimeter in diameter. The section of this latter shows a soft white tissue. Cut surface of the liver is of a uniform brownish gray color and of firm consistence. On close inspection numerous narrow grayish bands of connective tissues can be seen running along the lobules. This appearance is uniform and nowhere is there any marked connective tissue increase. On the cut surface a few small, grayish areas can be made out.

Gall bladder normal.

Kidneys show no evidence of metastases.

Uterus normal except for a few fibromyomata.

Tubes and ovaries normal.

Organs of neck: High upon the right side beneath the ramus of the jaw there is a tumor mass about 5 cem. in diameter, of firm consistence, which extends around to the internal carotid artery and reaches to the soft tissues posterior to the pharynx. In the region of the normal site of the thyroid no thyroid tissue could be found; the muscles apparently lie in close opposition to the trachea. Low down in the neck, just above the notch of the sternum, there is firm tissue similar to and continuous with that described in the pleura and which partially filled the anterior superior mediastinum, though there is no evidence of pressure on trachea or esophagus.

Larynx normal.

Esophagus normal.

Tongue normal. Trachea in lower half somewhat congested, otherwise normal.

ANATOMICAL DIAGNOSES.

Tumor of thyroid.

Extensive tumor growth in left pleura with hydrothorax and atelectasis of left lung.

Metastases in liver and lung.

Moderate cirrhosis of liver.

Fibromyomata of uterus.

MICROSCOPIC EXAMINATION.

Liver: There is a moderate diffuse increase of the connective tissue at the periphery of liver lobules. In

some lobules a considerable amount of fat is present in the liver cells in the peripheral half of the lobule.

Spleen: In some of the Malpighian bodies are small rounded masses of a hyaline material. In the pulp are scattered cells containing coarse granules of bright yellow pigment. Stroma not increased.

Kidney appears normal.

Tumor of neck: Nodule from submaxillary region is an adenoma papillomatous in character in most parts. In the simple parts we have small rounded spaces lined by a single layer of low cuboidal epithelium and filled with colloid. In the papillomatous parts ingrowth has taken place into larger spaces, so that they are almost completely filled by masses composed of a narrow connective tissue stalk, covered by epithelium similar to that lining the gland spaces.

Here the property of forming colloid is retained to a certain extent. Throughout the epithelium is regular and shows no evidence of rapid growth. The stroma in all parts is non-cellular and slow growing.

Tumor of pleura is of sarcoma type, made up of irregularly-shaped cells of varying size, the majority presenting a spindle shape. (Figs. 1 and 2.) However, there are many cells, round, oval or irregular in contour, large and small, some with one nucleus, others with several nuclei. In places large cells like giant cells can be seen. (Fig. 2.) In several places the spindle cells are quite closely packed, but for the most part the structure is loose and has very little intercellular substance to form a connective tissue stroma. Mitoses are numerous. The tumor forms a distinct layer along the pleura and everywhere invades the subpleural adipose tissue, the tumor cells arranging themselves in whorls around the fat cells. (Fig. 1.) The tumor is quite vascular and many small blood vessels

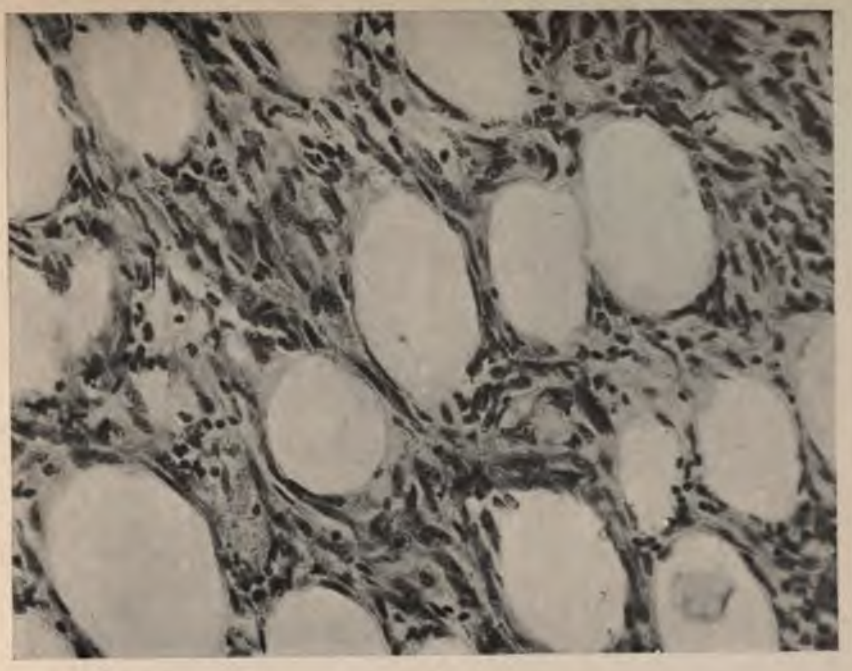

FIG. 1.

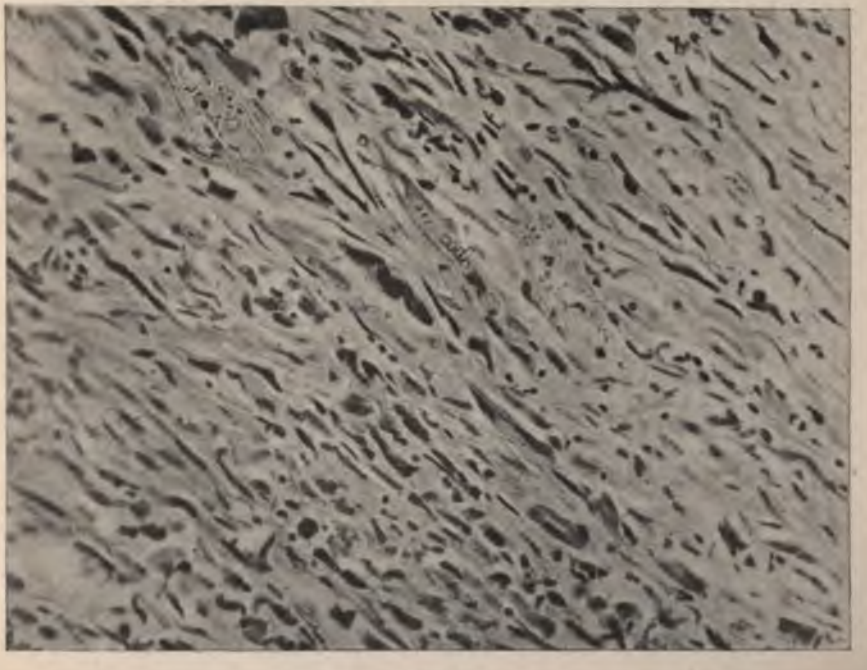

FIG. 2.

can be seen running irregularly through the tumor mass. These vessels are very irregular in shape. Tumor metastases in the lung are of same general type. The lung also shows an inflammatory process with leucocytes filling many alveoli. Tumor metastases in the liver are made up of the irregular cells with few of spindle shape and there is almost no stroma.

Tumors in uterus are both leiomyomata and fibromyomata. †

The literature contains very few references to sarcoma primary in the pleura, and by far the greater number of the reports are so meager and so indefinite that it is impossible to be sure of the primary site of the tumor or of its exact nature. A few reports are inaccessible to me.

The literature shows the following ten cases where the diagnosis can be made without reasonable doubt.

CASE I. Hofmokl[1] reports the following case in a child three and a half years old. Autopsy showed the left pleural cavity filled for the most part with a new growth consisting of numerous rounded masses varying in size from a half inch to three inches in diameter imbedded in dark red blood clot. The masses have the consistency of hard blood clot and are slightly resilient, their color is light to dark red, some slightly yellowish. On section they are red with yellowish-gray mottling. Blood vessels are small and thin walled. The whole tumor is enclosed in a sac of pseudo-membrane closely attached to the pleura. The tissue throughout the tumor consists of round cells

† I wish to express my thanks to Dr. Christian for his permission to report this case.

closely packed together. The ground substance cannot be seen except in places where it is nearly homogenous and slightly fibrous. Blood vessels thin walled, wide, and in places very numerous. Diagnosis: Round celled sarcoma.

CASE II. Regnault [2] reports the following case of primary sarcoma in left pleura in a man fifty-seven years old. Autopsy showed left pleural cavity contained five or six liters of clear fluid. Pleura, visceral and parietal, is covered with small tumors not ulcerated, varying in size from a few millimeters to 1½ ccm. On cutting these tumors a milky substance exuded. Examination of this substance showed round or oval cells with large nuclei. On section the tumors are formed of embryonal cells, closely packed without any interstitial substance. The majority of the cells are round with large nuclei. Some are oval and many show two prolongations at the poles.

CASE III. Schwalbe [3] reports a case in a woman of twenty-three. Autopsy shows large tumor, filling up whole of left pleural cavity. Section through tumor shows that left lung is surrounded by the growth. Surface of tumor smooth, reddish yellow and of firm consistence. Tumor consists of greatly thickened pleura, 4 cm. in thickness. Cut surface grayish-red in color. Fibrous structure in which there are many cells, round and spindle-shaped. Bronchial glands enlarged. Metastasis in left lung, right eye, diaphragm and liver.

CASE IV. Leube [4] reports a case in a man of thirty years of age. Diagnosis established at autopsy.

CASE V. Stewart and Adami [5] report a case in a man thirty-four years old. Autopsy shows a soft mass extending from upper extremity of left thorax down to level of sixth rib. Upper part of growth firmly at-

tached to costal pleura. Below where the border is free, the wall of the tumor is thick, dark blue in color, resembling a cyst containing blood. Heart displaced downwards and to left. The mass of tumor is very soft and on breaking capsule a large amount of semi-solid material of a dark purplish color easily passed out through the opening, about fifteen hundred cubic centimeters in all. The appearance is that of soft, breaking down blood clot. The mass is closely connected with the lung but no actual communication is demonstrable. Tumor thought to have started in a sac left after old adhesions. Microscopic examination shows lower mass almost pure blood clot. Denser parts show lobules of sarcomatous tissue. Many greatly dilated vessels of embryonic type in the denser tissue with very delicate walls. Cells are oval with oval well-staining nuclei separated in places by extravasation of blood. The costal pleura has undergone great fibroid thickening and infiltrated throughout with sarcoma cells.

Case VI. Kidd and Habershon [8] report a case of myxosarcoma in left pleura in a girl of eighteen. Autopsy showed an enormous mass filling left thorax; heart lying entirely to right of middle line. Pleural cavity almost entirely obliterated by soft spongy adhesions. Left lung displaced backward and almost entirely hidden. When the mass was removed it was seen to be a somewhat lobulated growth loosely attached to left upper lobe of lung and more firmly to lower lobe. The whole tumor is covered with a thin pleura-like membrane. On section the tumor is shown to consist of coarse fibrous network enclosing large blood cysts. Cystic spaces contain viscid puriform material and toward sternal border there are a few soft yellowish-white masses of growth. The blood cysts which were

a predominant feature of the growth contain fluid and coagulated blood. The softened puriform material on microscopic examination proved to consist of stellate and pyriform cells. Some sections show coarse fibrous net work enclosing red blood corpuscles in its meshes and many large thin-walled vessels filled with blood. In its more solid parts the growth is composed of closely packed round cells with very scanty stroma. Many of the individual cells contain clear rounded spaces or drops, apparently the result of mucoid degeneration. Many branching cells are seen with clear mucoid drops in them. No metastasis in any other organ.

CASE VII. Finlay [7] reports a case in a man sixty-seven years old. Autopsy showed bloody fluid in left chest. Left pleura easily stripped from chest wall. Both layers thickened, 5 mm. in thickness. Inner surface studded with nodules of white or reddish color, which on section are uniformly white and juicy. The nodules are from 5 mm. to 30 mm. in thickness, 8 to 60 mm. in diameter. Left lung is collapsed. One bronchial gland slightly enlarged, no metastasis in other organs. Microscopic examination shows the tumor to consist of large irregular-shaped, multinuclear cells with smaller round and oval cells between. Stroma not evident. Blood channels visible between rows of cells. Diagnosis, myeloid sarcoma.

CASE VIII. Kaufman [8] reports a case in a woman of twenty-nine years, where sarcoma, the size of a child's head, of soft consistency, was found in the right pleural cavity in the lower part. The diaphragm was involved in the growth. Microscopic examination showed a polymorphic cell sarcoma. The cell masses were arranged like mantels around wide thin-walled vessels. The vessels in many places were thrombosed and the

tumor tissue was necrotic in many places. Small metastases in spleen, kidney and liver.

CASE IX. Oelrick [9] reports a case in a man fifty-nine years old. Autopsy shows left lung pushed up to top of thoracic cavity entirely above third rib. Heart pushed to right beyond median line and the rest of the cavity taken up by a great sac formed by the pleura, which contained about three liters of a dark reddish semi-fluid material, which in lower part is more of a yellowish color and very sticky. The parietal pleura is greatly thickened and covered with nodules of tumor tissue and is infiltrated throughout with tumor cells. Microscopic examination shows growth to consist of a mixed cell sarcoma. The left lung contains metastases and there are metastases in pericardium, heart, right lung, liver and both kidneys.

CASE X. Busse [10] reports case in a man forty years old. Autopsy showed the right thorax filled with an enormous growth. The tumor is firmly fastened to the chest wall. The lung is completely surrounded by the growth. The growth consists of very thick pleura, one to three cubic centimeters on section. The inner surface showed rounded nodules, some of which are 10 cm. in diameter; in places the tumor is as hard as cartilage; in places there is calcification and also in many places softening with cysts in which there is myxomatous material. Upon section the tumor has a honeycomb structure. The septa are firm tissue in which are blood vessels. The tissue between the septa is made up of cells lying in a very homogeneous substance resembling hyaline cartilage, and with its consistency. In other places the tumor is softer and has the character of myxomatous tissue. The cells are round or oval with large nuclei and easily staining protoplasm.

Diagnosis: Chondro-myxo-sarcoma.

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GENERAL STREPTOCOCCUS INFECTION THROUGH UNRECOGNIZED CHANNELS: A REPORT OF TWO CASES.

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STREPTOCOCCUS septicemia is not apt to be considered in the differential diagnosis of a case which does not present signs of local sepsis or chronic wasting disease. The following cases are presented to show the diagnostic importance of streptococcus septicemia in cases of obscure and severe infection.

CASE I. W. W. F. was admitted to Dr. Fitz's wards in the Massachusetts General Hospital on Jan. 11, 1908, and gave his history as follows: He was an American, white, thirty years of age, married, a waiter by occupation.

Family history: Father died at sixty-three of Bright's disease. Mother died at fifty-four of asthma and bronchitis. Wife and three children well. Two children died in infancy. One other child died of trauma. No history of consumption.

Past history: He remembered no past diseases excepting gonorrhea ten years ago. He had concussion of the brain several years ago after being kicked in a gymnasium. Appetite, sleep, bowels, micturition, normal.

Habits: Five cups of tea a day. No coffee, little alcohol. Seldom smokes.

Present illness: Seven days before entrance he went

to bed at night feeling well. He awoke at 3 A.M. in a chill, shivering so that he shook the bed. During the remainder of the night he had frequent chills, but he did not feel feverish or sweat. He remained in bed until noon, when he rose feeling almost well. The following morning he went to work, but he soon fainted. He was brought home and put to bed where he remained. Two days before entry he rose from the bed and fainted. For five days before entrance he had felt feverish. He had no cough, sore throat, pain in chest or vomiting. Bowels were constipated for a few days. Urine dark in color. On the morning of the day of entrance he had considerable tenderness and some pain in his left lower leg.

Physical examination: The patient entered the hospital with a mouth-temperature of 100.4°, a pulse of 104, and respiration of 20. He was abnormally alert, slightly delirious, and talkative. He was willing to lie quietly in bed and was able to give his own history. All his motions were tremulous.

He was well developed and nourished. His skin and mucous membranes were moderately pale. His skin was hot and he perspired freely. His pupils were equal and reacted to light and distance. His tongue was dry and clean in the anterior portion, coated and white in the posterior. The pharynx was dry and bright red. Teeth good, several missing.

His heart was normal in size, and the sounds were of fair quality, regular and rapid. No endocardial murmurs. The radial pulse was regular, rapid, of small volume, and of very low tension. Artery wall was not palpable.

The lungs were normal.

The abdomen presented nothing abnormal. Liver and spleen were not made out to be enlarged.

He had slight hypospadias. His knee-jerks were normal. The plantar reflexes were not obtained.

Scattered over his extremities were the following lesions. The extensor surface of his right upper arm was red, swollen and tender. The circumference of the right upper arm was 10½ in.; of the left, 9½. Just below the external condyle of the right humerus was a fluctuant swelling 1½ in. long, not red or tender. Just below the right elbow on the inner surface was a dark brown, slightly tender spot, ½ in. in diameter, surrounded by diffuse swelling and tenderness, extending 3 in. below the spot and up to the elbow. There was a similar small brown spot 3 in. above the right elbow on the extensor surface. Over the right ulna, just above its middle, was a red, firm, tender swelling half an inch in diameter. On the back of the right hand from the wrist to the middle finger was a red, slightly tender, fluctuant swelling 2 in. wide. The fingers and wrist can be moved with slight pain. On the back of the left hand near the wrist was a red, fluctuant swelling 1 in. in diameter.

On the right buttock near the thigh was a flat reddened area half an inch in diameter and slightly tender. Just above the right popliteal space was a similar spot, which was not tender. In the middle of the left shin was an area 4 in. long of moderate edema, slight redness and considerable tenderness. This area extended inward so as to include the middle third of the inner aspect of the lower leg. In this area, 1 in. to the right of the tibia, was a round, dark, brownish-red spot, 1 in. in diameter, slightly whitened at the center, very tender. The circumferences of the calves 3½ in. below the tubercles of the tibiæ were, right 11 in., left 12½ in.

Progress of case. — A few hours after admission the patient's rectal temperature was 104.4°, his pulse 108,

and his respirations 32. His hemoglobin by the Talqvist scale was 90%. His leucocyte count was 8,000. He became more delirious and tried to get out of bed. He was talkative, affable and mentally stimulated. He lived about fourteen hours after entrance, and during that time his rectal temperature rose steadily to 107.5°, his pulse rate to 180, and his respirations to 52. His pulse grew progressively weaker and was not palpable at the wrist for four hours before death. Almost up to his very death, long after his forearms and lower legs were pulseless, blue and cold, the patient's mind was alert, his eyes bright, and his face smiling, and he was talkative and delirious.

A blood culture was taken immediately after death. The blood was withdrawn from a vein under unfavorable circumstances. Both streptococci and staphylocci developed in the culture.

Autopsy. — The autopsy was performed by Dr. Oscar Richardson, seven and three-fourths hours postmortem.

The meninges, vessels of Willis, sinuses, middle ears and brain were not remarkable.

The skin presented many small and large areas of purplish-red discoloration. The lesions described in the physical examination at entrance were but little changed except that they were purplish and some were larger. Section into the lesion in the vicinity of the right knee showed that the deep tissues were infiltrated with sero-sanguineous, gelatinous-like fluid. The muscle tissue in this situation was dark, sloppy and looked as if it were somewhat necrotic. On opening the right knee-joint much sero-sanguineous gelatinous-like fluid escaped. A cover-glass smear taken from this fluid showed on microscopical examination many streptococci. Section into the lesion of the left lower leg

showed a condition similar to that in the tissues in the region of the right knee. Section of the tibia showed nothing remarkable in the bone or in the marrow.

Subcutaneous fat moderate in amount. Muscles not remarkable.

Peritoneal cavity free from fluid. Peritoneum, appendix, position of liver, diaphragm, not remarkable.

Pleural cavities free from fluid. The lungs were bound down everywhere by old membranous fibrous adhesions. The bronchial lymphatic glands, the tongue and the larynx were not remarkable. The trachea and bronchi contained a moderate amount of bloody, mucus-like material. In the upper part of the upper lobe of the right lung there was a fibrous, indurated mass about 5 cm. in each dimension. The mass showed, scattered through it, smaller and larger fibro-calcareous masses. The apex of the left lung showed a similar mass. The lungs elsewhere showed no areas of consolidation, but they were infiltrated with considerable blood-like material.

Pericardium not remarkable. Heart weighed 240 gm. The heart was rather small. On section the myocardium was firm and slightly pale and cloudy. The valves and cavities were not remarkable. The foramen ovale presented an oval opening about 1 cm. in its greatest dimension. Coronary arteries free and smooth. The aorta showed a smooth intima with areas of purplish staining.

The liver weighed 1,530 gm. On section the tissue was firm, rather homogeneous and of pale, brownish-yellow color. No stones in gall bladder. Bile ducts free. Pancreas and duct of Wirsung not remarkable. The spleen weighed 135 gm. and was purplish and mushy. Adrenals not remarkable.

The right kidney weighed 114 gm. The capsule was stripped easily, leaving a pale surface with areas of depression. On section the pelvis showed moderate dilatation. Several of the calices were considerably dilated, and the calices generally showed moderate dilatation. About the calices which were most dilated there was considerable atrophy of the kidney tissue. In places only a narrow layer of the cortical portion of the kidney remained. The small areas of depression noted above were over the atrophied portions of the kidney. The markings of the kidney were plain. The section surfaces were somewhat purplish and cloudy. The pelvis contained a moderate amount of thin cloudy fluid. The first portion of the right ureter was slightly dilated, and at a point about 3 cm. from the pelvis, this ureter was completely occluded by an ovoid stone, measuring about 1.5 cm. in greatest dimension. The left kidney was not remarkable except for the section being purplish and cloudy.

Bladder, prostate, seminal vesicles and testes on section were not remarkable. In the situation of the urinary meatus there was a deep crevice-like depression which ended blindly and had no communication with the urethra. The urethra opened in the skin a little below this crevice.

Esophagus, stomach and intestines presented no lesions.

Cultures on blood-serum culture medium from the heart's blood, the spleen, the tissues of the right knee, and from the right knee joint showed profuse growth of the streptococcus pyogenes.

Anatomical diagnosis. — Septicemia (streptococcus), phlegmon of left leg, right knee and right hand. Soft spleen. Stone in the right ureter with occlusion of ureter. Hydronephrosis of the right kidney, chronic

pleuritis, obsolete tuberculosis of the lungs, hemorrhagic edema of the lungs. Defective closure of the foramen ovale. Hypospadias.

The above report of the autopsy has been condensed from Dr. Richardson's record.

CASE II. A little girl, one and one-half years old, was brought into the accident room of the Massachusetts General Hospital on the evening of Jan. 27, 1908, and was admitted to the wards of Dr. Fitz. The parents were Russian Jews. The child was born in Boston.

Family history: Father, mother and sister well. No history of tuberculosis.

Past history: Child had been well and plump since birth. She ate, slept and moved her bowels normally. She seemed perfectly well up to day of entrance.

Present illness: In the early morning she felt cold and shivered and later seemed feverish. She was fussy during the day, and she vomited once in the afternoon. Her bowels moved twice during the day and the stools were loose and somewhat green and slimy. No cough or coryza or convulsions.

Physical examination: A plump, well-developed child. Skin and mucous membranes of good color. Child lay on accident-room table with head slightly retracted and back straight. Temperature by rectum was 103.5°, pulse 180, respirations 44. Anterior fontanelle was about 1 in. in diagonal diameter, not bulging. Pupils equal and react to light. Movements of eyes normal, except for an occasional quiver of the eyeballs. Nostrils showed a few dry crusts. Alæ nasi moved with respiration. Four teeth, two upper and two lower. Tongue was bright red and clean at the tip, coated in the posterior part. The throat was bright red, otherwise normal.

Heart not enlarged. Sounds regular, rapid, of

good quality, no murmurs. Pulses synchronous, equal, regular, of good volume and tension.

Lungs were normal.

Abdomen was normal in appearance, soft, tympanitic. There were no masses or tenderness. The liver dullness extended from the sixth rib to ½ in. below the costal margin, where the edge was indistinctly felt. The splenic dullness measured 1¾ by 1¼ in., and the edge was not palpable.

The knee-jerks and plantar reflexes were normal. Kernig's sign was absent. No edema. No enlargement of lymphatic glands was made out. There was slight redness and roughening of the skin over the buttocks and thighs. There were many small excoriated papules on the skin of the body and limbs, including the soles of the feet.

A stool passed during the physical examination was small, soft, greenish-white, and contained considerable mucus.

The child cried when her head was brought forward into line with her body. Pressure on the back of her neck caused spasmodic movements of her legs and made her cry out as if in pain. Occasionally the child made a spasmodic movement of its body. The child was conscious, but she paid little attention to her surroundings.

During the examination the child had a severe convulsion, lasting about three minutes. The whole

theless, the child grew progressively worse. On the day after entrance her neck was flaccid and not retracted, and it remained so. The child frequently held its arms rigid, sometimes with its elbows, wrists and fingers flexed. At times her breathing or crying was stridulous, suggesting stenosis of the trachea or larynx. The thymus dullness measured 1¾ by 1⅛ in. Dr. A. Coolidge, Jr., saw the case in consultation and reported that the pharynx and larynx were reddened and that otherwise there was nothing definite found in the throat or larynx. Dr. H. L. Morse reported on the condition of the ears as follows: "Ears negative as a cause for temperature. Membrani both pink. Left one pricked. No fluid obtained." Culture from the throat was negative for the diphtheria bacillus and showed streptococci and staphylococci as predominating organisms. Lumbar puncture done on the day of her death showed a clear fluid with a few shreds, no cellular elements, no bacteria, negative culture.

The temperature rose irregularly to 106.5° and fell to 104° on the day of her death, the sixth day of the disease. The pulse rose to 205 and the respirations fluctuated between 40 and 60. On the day of death the pupils became unequal, a conjunctivitis appeared in the right eye, and the spleen was made out to be enlarged to percussion. The child seemed blind and deaf, but was annoyed when moved. No stiffness of neck.

Immediately after death a blood-culture was taken, the blood being withdrawn from the heart with a long needle. Autopsy was refused.

The blood culture showed an abundant growth in pure culture of the streptococcus pyogenes.

The occurrence of these two cases in Dr. Fitz's wards in the same month raised the ques-

tion whether streptococcus septicemia without discoverable point of entry and without preceding severe disease was not much more common than generally supposed. Search through the records of one thousand autopsies done in the Massachusetts General Hospital between Oct. 19, 1896, and Jan. 13, 1903, revealed no such case. In about one tenth of the cases cultures were not taken from the heart's blood. Streptococci were found in the heart's blood in 76 cases; in pure culture in 62 cases, and accompanied by other organisms in 14 cases. Not one of these cases was free either from some evident point of entry for the infection, as a wound, ulcer or abscess, or else from some severe and, in most cases, chronic disease for which the septicemia was terminal. Among the 62 cases which gave pure cultures 41, or about two thirds, had suppurating foci or wounds to explain the infection, and in the remaining 21 the infection was terminal to some severe disease. Of the 14 cases of mixed infection all but one showed a suppurating point or a wound. Thus it appears that a streptococcus blood infection is usually uncomplicated by the presence of other organisms when the infection is through some unknown portal and that, on the other hand, when there is a wide gateway such as an open wound or an abscess, more than one variety of bacterium are apt to enter.

In each of the cases reported a healthy person was taken sick and died of profound toxemia within eight days from the onset. One case

showed the beginning local suppuration of pyemia, but the abscess stage was not reached. In both cases clinical observation, and, in one, autopsy failed to reveal the source of infection. Both patients had inflamed throats which may have been the place of entrance, but it seems plausible that the throat affection was secondary.

Although the infection of the blood with streptococcus is rare except as a complication, the differential diagnosis in obscure cases of severe infection is incomplete without consideration of streptococcus septicemia.

THE ORIGIN OF URINARY CASTS; AN EXPERIMENTAL STUDY.

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IT has been demonstrated by a good many experimenters that kidney lesions simulating very closely nephritis in man may be produced in animals by the injection of various irritants. Only a few of these investigators, however, have given any account of the urinary findings, with special reference to casts, or of the origin of casts from the diseased kidney. Wallerstein[1] reports from studies of experimental nephritis in rabbits that urinary casts arise from epithelial cells, and that hyaline casts are an end result in the process of cell necrosis and degeneration.[2] The experiments here reported were undertaken at the suggestion of Dr. Henry A. Christian and were carried out in the division of the laboratory of the Department of the Theory and Practice of Physic, which is under his direction. The work was done in the hope of throwing further light on the question of cast formation.

The irritants used for producing nephritis were

[1] Zeitschr. für klin. Med., 1906, lviii 296.
[2] For the recent literature on experimental nephritis, see Christian: Theory and Practice of Medicine, BOSTON MED. AND SURG. JOUR., 1908, clviii, 416.

the same as those employed by previous experimenters for this purpose, with the addition of trypan red. All were given subcutaneously. Uranium nitrate was the first substance used, and it proved the most satisfactory. It was given in doses varying from one to five milligrams, but preferably in repeated doses of one milligram rather than in a single larger dose, since some of the animals were unable to survive one dose of one milligram. Potassium bichromate was given in doses of one half to one cubic centimeter of a 5% solution. Trypan red was used in saturated aqueous solution in doses of from one to five cubic centimeters. Arsenic was administered as Fowler's solution, in one to five minim doses. The last drug employed was cantharidin, given in doses of one milligram of a 1 to 2,000 solution.

Rabbits were used in all the experiments. They were kept in cages having an inclined bottom leading to a center, and by a tube into a bottle, so that all the urine was collected. Urinalysis was done daily, but only the excretion of albumin and casts was studied with any degree of thoroughness. It was often found difficult, in fact impossible in some cases, to get the urine perfectly clear. The presence of large numbers of bacteria, whose growth is favored by the alkaline urine, together with the precipitates of carbonates and phosphates, is largely responsible for this turbidity. Antiseptics were put into the collecting vessels with the hope of inhibiting the growth of bacteria, but the result was not gratifying. If

a strong acid is added to the urine to neutralize it, such a violent reaction occurs with the liberation of CO_2 as to destroy the casts and interfere with filtration. The turbidity was most satisfactorily overcome by adding to the urine to be centrifugalized a small amount of very dilute acetic acid solution. This is not strong enough to cause the liberation of CO_2 and yet helps very much in the examination of the sediment. To get the urine clear for determining albumin, the same dilute acetic acid was used and the urine filtered several times if necessary. Care must be taken not to add too much acid, a drop or two in a half wineglass of urine is usually sufficient, for the urine becomes turbid again with an excess of acid.

Each animal was watched for a day or two when first put into the cage before it was given any injections, for it is well known that in confinement rabbits often show albuminuria and cylindruria. In every instance the rabbit was allowed to become albumin- and cast-free before starting the experiment. To prove that this was necessary a rabbit which had received no injections, but had albumin and casts in the urine, was killed, and the kidney on section showed marked cloudy swelling of the epithelium of many of the convoluted tubules in certain areas, but this process was not as general as in the earlier stages of the toxic nephritis, and no tubules showed actual necrosis.

In general, the examination of the urine for albumin did not reveal anything remarkable. In regard to the appearance of casts, however, it is to

be noted that the fine, granular casts were the first to appear in every instance, with one or two exceptions. The hyaline casts came later. There was a greater variation in the size and shape of the casts than is commonly seen in human nephritic urine, and there was a tendency for the casts to appear in showers, only a few or even none might be seen on one day and great numbers the next. These cast-showers were usually accompanied by a corresponding rise in the quantity of albumin. As one would expect, the animals in which the main kidney lesions were glomerular did not show so many casts in the urine as those in which the tubules were primarily affected, but they did show a relatively large amount of albumin.

Whenever possible, the animal was killed, not allowed to die, and by this means post-mortem changes were eliminated and the better sections from fresh tissues were secured. In this study the description of the kidney sections was limited to those phases of the process associated with cast formation and many epithelial changes and cellular infiltrations neglected, as they had no bearing on this particular phase of the subject. It is hoped that a careful study of the sections may be reported at some other time. All tissues were hardened in Zenker's fluid and embedded in paraffin. The sections were stained with eosin and methylene blue.

URANIUM NITRATE.

The various stages of the process of cast formation were clearly shown in the kidney sections

from animals which had received injections of this drug. The first change noted was a swelling of the cells composing the convoluted tubules, by which process the cell boundaries are lost and the lumen of the tubule obscured. (Fig. 1.) The straight tubules were also affected in a similar manner, but to a much less extent. From this swelling the cells went on to a marked degeneration in which the whole tubule often became destroyed and in its place there remained a granular necrotic mass, staining a dark pink with eosin and methylene blue. (Fig. 2.) Scattered through this mass the cell nuclei could be made out, often nearly normal in appearance, but in many instances altered so that their fine, reticular structure was entirely lost and the chromatin granules massed together in a single dark speck. The distal convoluted tubules appear to be affected by the degenerative changes earlier than are the proximal. This is shown in Fig. 8, in which an almost normal tubule is seen at its origin from a glomerulus, whereas tubules more distant show degenerations. Later, both groups of convoluted tubules show injury. At this stage of the process there were no casts to be seen in the collecting tubules, showing that their origin is not co-incident with the lesions in the convoluted tubules, but is dependent upon it. These stages are well illustrated in many of the animals and are seen exclusively in those given a single injection and killed at the end of twenty-four hours.

The following are illustrative protocols:

Rabbit No. 5. First day. 1,040 gm., rabbit caged.

Second day. Urine showed no albumin, no casts. Given .005 gm. of uranium nitrate subcutaneously.

Third day. Urine showed albumin, very slight trace. No casts. Animal killed.

Kidney: macroscopically normal. Microscopically, glomeruli apparently normal. Cells lining the convoluted tubules necrotic, many times cell boundaries completely lost and lumen filled with a granular material. The nuclei are very prominent, some of them have lost their characteristic appearance and look simply like a dark mass, with eosin and methylene blue stain. No fine reticular structure can be made out. The collecting tubules do not show any variation from the normal, their lumen is free from granular material.

Rabbit No. 2: First day. 635 gm., rabbit caged.

Second day. Urine: no albumin, no casts.

Third day. Urine: no albumin, no casts.

Fourth day. Urine: no albumin, no casts. Given .004 gm. uranium nitrate subcutaneously.

Fifth day. Urine: albumin, slight trace. Rare cast with cells adherent. Given .004 gm. uranium nitrate subcutaneously.

Sixth day. Urine: albumin, slight trace. Rare granular cast.

Seventh day. Urine: albumin, slight trace. Few granular casts. Animal found dead.

Kidney: Macroscopically, dark colored and the markings distinct. Microscopically, glomeruli apparently normal. Convoluted tubules everywhere necrotic, cell boundaries and lumen indistinct; in many places the whole tubule is a mass of granular material with nuclei scattered through it. Epithelium of collecting tubules normal. In some of the tubules at some distance from cortex the lumen contains the degen-

erated cells, but less granular in appearance, and only rarely is a nucleus seen. These tubules take deeper stain with eosin and methylene blue stain.

Rabbit No. 9. First day. 930 gm., rabbit caged.

Second day. Urine: no albumin, no casts. Given .002 gm. uranium nitrate.

Third day. Urine: no albumin, no casts.

Fourth day. Urine: no albumin, no casts. Given .002 gm. uranium nitrate.

Sixth day. Urine: albumin, trace, occasional granular cast, some with cells adherent.

Seventh day. Urine: albumin, large trace, rare granular cast.

Eighth day. Urine: albumin, slight trace, no casts. Animal found dead.

Kidney: Macroscopically, appears slightly pale, seems boggy. On section tissue is injected, but markings are distinct. Microscopically, glomeruli appear normal. In cortex convoluted tubules are necrotic; in some places there is almost no evidence of the lumen, and when intact the lumen is often filled with granular detritus. The straight tubules are involved in the destructive process to a slight extent. The epithelium of the collecting tubules is mostly intact, but the lumen often contains a granular plug or cast.

A further stage in the process of cast formation was seen in tubules in which the epithelium was necrotic, but the cell boundaries remained for the most part distinct. The lumen of those tubules was preserved, but filled with a granular detritus similar in appearance to the material composing the necrotic cells lining the tubules. Apparently this was the result of the necrosis of

the cells of the tubules, for it was not found in a single mass, but was broken up into segments or sections representing in outline degenerated epithelial cells, and most of these had a darkly staining mass within them, the remnant of a destroyed nucleus. (Fig. 3.)

The following animal illustrates this point well:

Rabbit No. 1. First day. 1,350 gm., rabbit caged.

Second day. Urine: no albumin, no casts.

Fourth day. Urine: no albumin, no casts. Given .005 gm. uranium nitrate.

Fifth day. Urine: albumin, trace. Few casts, some of them only very slightly granular, with cells adherent. Very rarely an epithelial cast. Given .005 gm. uranium nitrate.

Sixth day. Urine: albumin, large trace. Considerably many granular casts, rarely with cell adherent. Given .005 gm. uranium nitrate.

Seventh day. Urine: albumin, large trace. Numerous granular casts, some with cells adherent.

Kidney: Macroscopically, firm and pale. Markings not very distinct. Microscopically, glomeruli appear normal. Epithelium of the convoluted tubules necrotic, cell boundaries and lumen often obscured. Certain tubules, especially those removed from the cortex, are better preserved and their lumen filled with granular material. This is often separated into irregular divisions, appearing like the remnants of cell divisions, and partially degenerated nuclei may be seen within the segments. Some tubules, themselves normal, contain a nearly homogeneous mass, separated from the lining epithelium by a clear space, evidently a hyaline cast. Collecting tubules are normal, but contain a good many casts.

The next stage in the process of cast formation was seen in sections which show in the tubules farther removed from the cortex a much less marked necrosis of the epithelium, but the lumen contains granular material. This had lost its sectional or broken-up appearance and the necrotic remains of the individual cells had become much more closely massed together, though in many instances the cell boundaries could be distinguished. (Fig. 4.) Next, the cast appeared as a very finely granular mass in which no remnant of the cell origin was evident (Fig. 5), and finally the granular characteristic of the casts was less prominent and the hyaline nature appeared. (Fig. 7.) It is interesting to note that the more granular the cast the less well preserved was the epithelium of the tubule in which it was found. The necrotic material coming from the convoluted tubule is apparently forced along by the urinary stream and molded into shape by the tube through which it passes. At first the detritus is very loosely formed and coarsely granular, but as it passes down the tubule it comes together into a compact mass and becomes more finely granular and eventually hyaline. It is possible also that some change is taking place at the same time in the material which composes the cast and that this results in a fusion of the original granular substance into a homogeneous mass. Certain sections showed cells attached to the granular plug within the lumen of the tubule. (Fig. 6.) These appear to have been deposited on

the partially formed cast as it moved downward in the urinary stream.

This stage is shown in the following animals:

Rabbit No. 3. First day. 825 gm., rabbit caged.

Second day. Urine: no albumin, no casts. Given .004 gm. uranium nitrate.

Third day. Urine: albumin, very slight trace. Very many granular casts, occasionally with cells adherent. Given .004 gm. uranium nitrate.

Fourth day. Urine: albumin, trace. Many casts, many with cells adherent. Given .004 gm. uranium nitrate.

Fifth day. Urine: albumin, trace. Few granular casts. Animal killed.

Kidney: Microscopically, pale, rather firm and edematous, markings moderately distinct. Microscopically, glomeruli apparently normal. Convoluted tubules near the cortex very necrotic, the lumen destroyed, and tubule replaced by a finely granular mass with nuclei fairly well preserved. Farther from the cortex the epithelium of the tubules is somewhat less necrotic, but for the most part granular, and the lumen contains a granular plug. The collecting tubules show a normal epithelium, but casts within the lumen separated from the lining cells by a free space. The casts in some instances appear like swollen, degenerated cells, the boundaries between which can be faintly made out and the remnants of nuclei seen.

Rabbit No. 7. First day. 1,020 gm., rabbit caged.

Second day. Urine: no albumin, no casts. Given .005 gm. uranium nitrate.

Third day. Urine: albumin, slight trace. Considerably many granular casts, occasionally with cell adherent.

Fourth day. Urine: albumin, large trace, many granular casts.

Sixth day. Urine: albumin, large trace, many granular casts.

Seventh day. Urine: albumin, slight trace, no casts. Animal killed.

Kidney: Macroscopically, slightly pale. Markings distinct. Microscopically, glomeruli appear normal. Cells of convoluted tubules are necrotic, but lumen is fairly well preserved; many casts in collecting tubules, many of them showing cells adherent. A considerable number of casts are denser and darker staining. Many mitotic figures are seen throughout the section.

The epithelium of the collecting tubules was in most instances normal, but the lumen contained casts carried along by the urinary stream. These casts appeared much more uniformly granular and were entirely distinct from the lining of the tubules, being separated from it in most instances by a clear space. Occasionally the cast had lost its granular appearance and become homogeneous, taking a darker stain with eosin and methylene blue; in other words, it was a hyaline cast.

The following animal showed this:

Rabbit No. 11. First day. 985 gm., rabbit caged.

Second day. Urine: no albumin, no casts. Given .001 gm. uranium nitrate.

Third day. Urine: no albumin, no casts.

Fourth day. Urine: albumin, slight trace, many fine granular casts.

Fifth day. Urine: albumin, slight trace, many fine granular casts:

Sixth day. Urine: albumin, trace, few granular casts, some with cells adherent. Animal dead.

Kidney: Macroscopically, rather dark, markings distinct. Microscopically, glomeruli apparently normal. Convoluted tubules show necrosis of the epithelium as in previous sections, but in much less marked degree. Collecting tubules contain only a very few casts, but these are separated from the lining epithelium by a clear space and are not connected with those cells in any way. The casts are for the most part granular, but occasionally hyaline.

The kidney sections from an animal [3] allowed to run for a long time showed very different lesions, simulating closely those of chronic interstitial nephritis. There was considerable increase in the connective tissue, much dilatation of the tubules and glomerular spaces and some apparent increase in the cellular elements of the glomerular tufts. (Figs. 9 and 10.) The convoluted tubules which were not dilated showed some necrosis. In these the lumen was mostly obscured and the tubule filled with the granular material as described in connection with the more acute processes. Only a very few of the collecting tubules showed any casts, and those present were much more homogeneous in appearance, a few were hyaline.

This animal showed the following:

Rabbit No. 10. First day. 800 gm., rabbit caged. Second day. Urine: no albumin, no casts. Given .001 gm. uranium nitrate.

[3] In this case a spontaneous chronic lesion cannot be absolutely excluded. Confirmation of other experiments is needed to prove the assumed relation between the uranium and the lesions.

Fourth day. Urine: no albumin, no casts. Given .001 gm. uranium nitrate.

Sixth day. Urine: albumin, trace. Rare fine granular cast. Given .001 gm. uranium nitrate.

Seventh day. Urine: albumin, trace. Rare fine and coarse granular cast.

Eighth day. Urine: albumin, trace. Very rare cast.

Ninth day. Urine: albumin, large trace. Very rare granular cast.

Tenth day. Urine: albumin, trace. Occasional granular cast.

Eleventh day. Urine: albumin, very slight trace. Occasional granular cast.

Thirteenth day. Urine: albumin, very slight trace. Occasional granular cast.

Fifteenth day. Urine: albumin, slight trace. Rare hyaline cast.

Seventeenth day. Urine: albumin, slight trace. Rare hyaline and fine granular cast.

Nineteenth day. Urine: albumin, slight trace. Very rare granular cast.

Twentieth day. Urine: albumin, slight trace. Occasional granular cast.

Twenty-first day. Urine: albumin, slight trace. Rare fine granular cast.

Twenty-third day. Urine: albumin, slight trace. No casts.

Twenty-sixth day. Animal killed.

Kidney: Macroscropically, small, pale, slightly granular and markings not very distinct. Microscopically, considerable increase in the connective tissue and in the cellular elements in the glomerular tufts. The tubules are much dilated and there is an increase of the space within the capsule of the glomeruli. The epithe-

lium of the convoluted tubules which are undilated show a fair amount of necrosis, with obscuring of the lumen and filling of the tubule with granular material as seen before. Only a few of the tubules show any casts, but they are more homogeneous than in other sections and a few are hyaline.

POTASSIUM BICHROMATE.

Potassium bichromate produces lesions which in the main are like those of uranium nitrate; that is, the convoluted and straight tubules are attacked and the glomeruli remain normal. In most cases with potassium bichromate there was a more general destruction of the tubular epithelium, and in some instances the collecting tubules were also involved in the necrosis. The process of cast formation could be seen here also. The granular detritus coming from the broken-down epithelial cells of the convoluted tubules was massed together and had taken on the form and shape of the tubule through which it passed. In the early stages of the process, and high up in the secretory system, the casts were always granular, but later and farther along they became either more homogeneous or truly hyaline.

These animals are typical of a number of experiments with injections of potassium bichromate.

Rabbit No. 30. First day. Rabbit caged.

Second day. Urine: no albumin, no casts. Given 1 ccm. of 5% solution of potassium bichromate.

Third day. Urine: albumin, slight trace. No casts. Animal killed.

Kidney: Macroscopically, normal in appearance. Microscopically, glomeruli appear normal. Marked necrosis of the convoluted tubules and to slight extent of straight tubules. Often there is complete destruction of the tubules and the place taken by a granular mass with nuclei in the midst. No casts seen in collecting tubules.

Rabbit No. 12. First day. Rabbit caged.

Second day. Urine: albumin, slightest possible trace. No casts.

Third day. Urine: albumin, slightest possible trace. No casts.

Fourth day. Urine: albumin, slightest possible trace. No casts. Given ½ ccm. 5% solution of potassium bichromate.

Fifth day. Urine: albumin, very slight trace. Very rare granular cast.

Sixth day. Urine: albumin, very slight trace. Occasional granular cast.

Seventh day. Urine: albumin, very slight trace. Occasional fine and coarse granular cast.

Eighth day. No urine. Animal found dead.

Kidney: Microscopically, glomeruli apparently normal. Very widespread destruction of tubular epithelium, only few areas where there is normal epithelium The convoluted tubules are necrotic and lumen obscured, their place being taken by granular material. The straight tubules are less affected, though some of them are granular in appearance and the lumen is usually filled with casts in the process of formation. The collecting tubules contain many granular casts and a rare hyaline cast; these latter are always in tubules whose epithelium is normal.

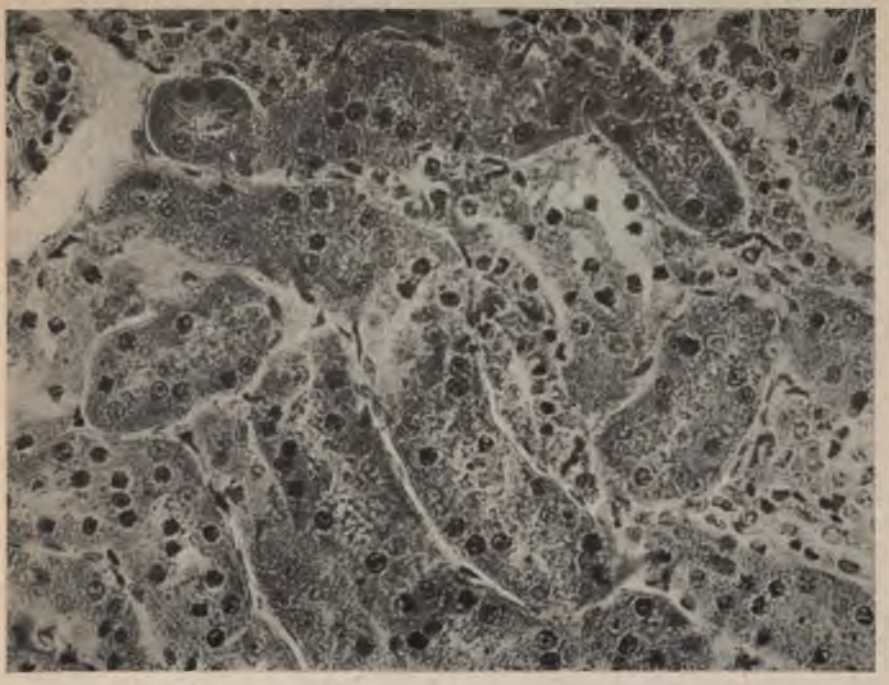


FIG. 1.

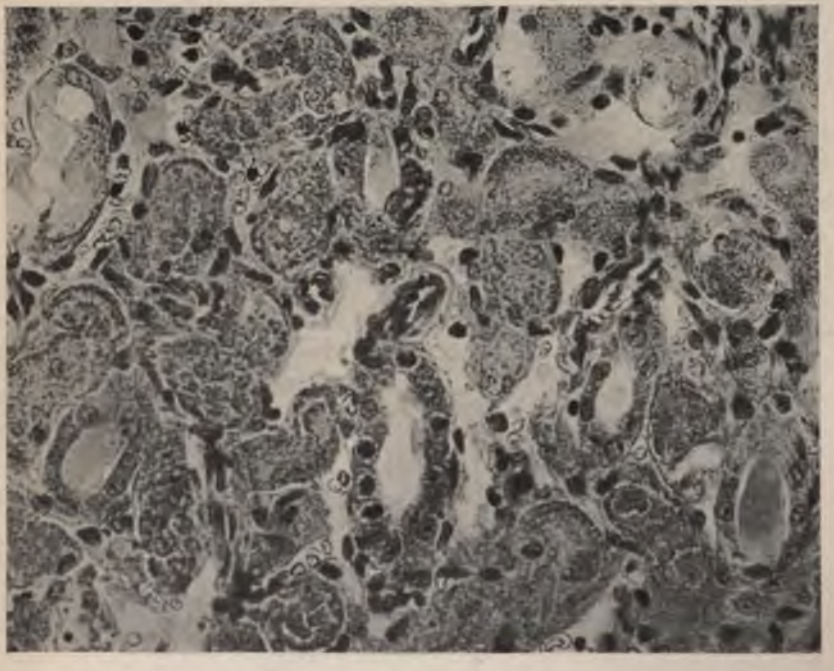


FIG. 2.

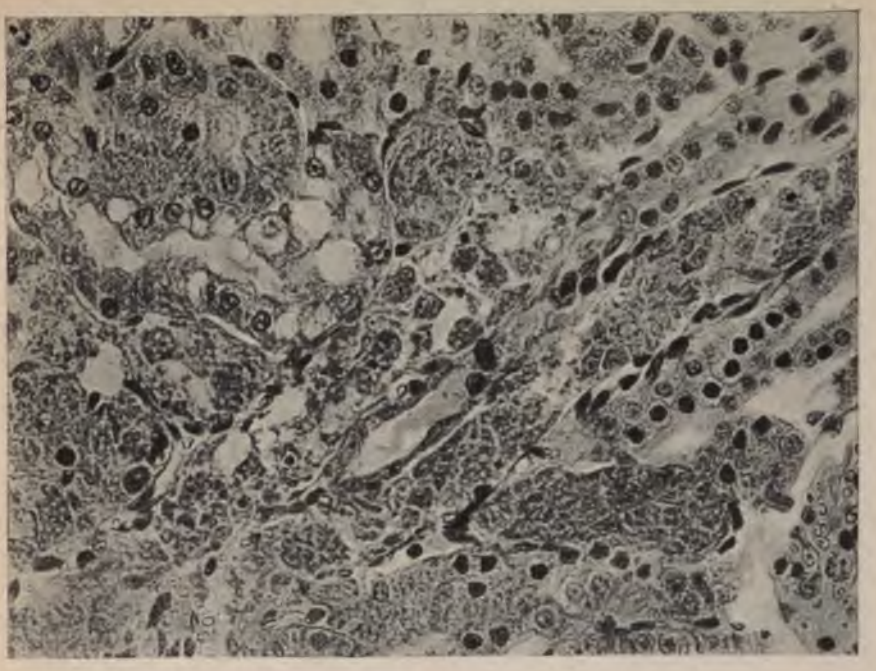


FIG. 3.

FIG. 4.

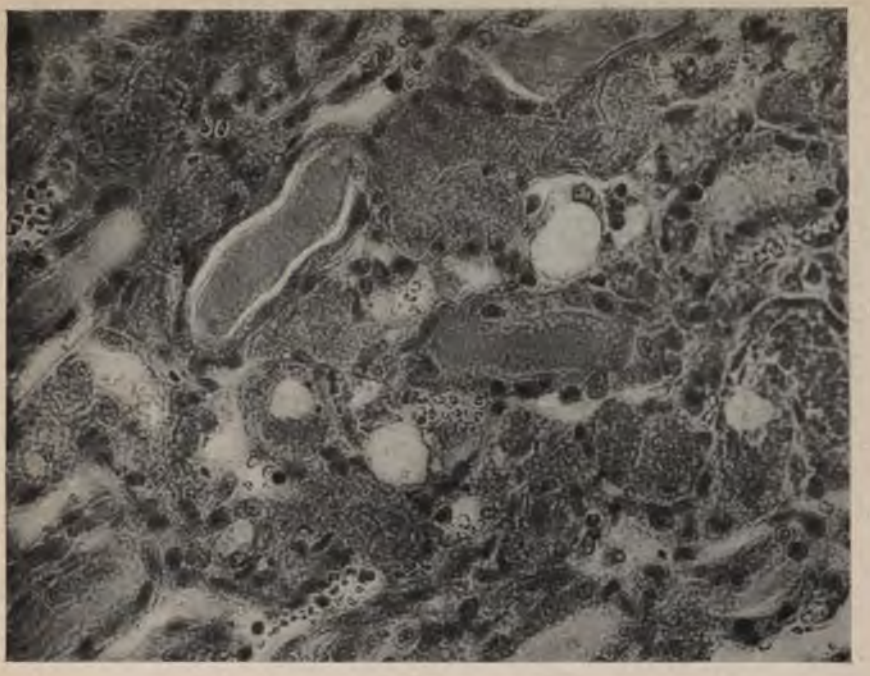


FIG. 5.

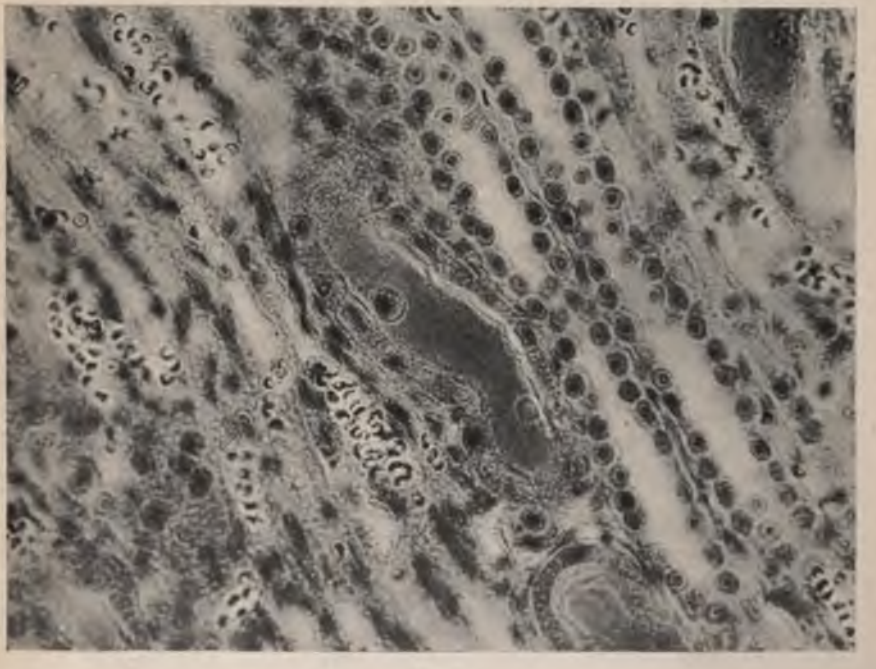


FIG. 6.

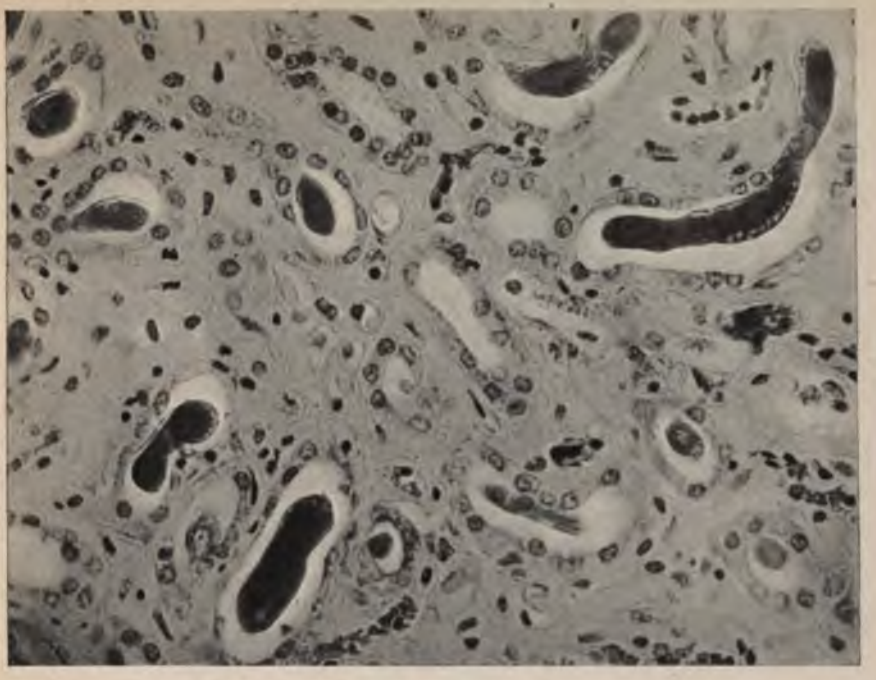


FIG. 7.

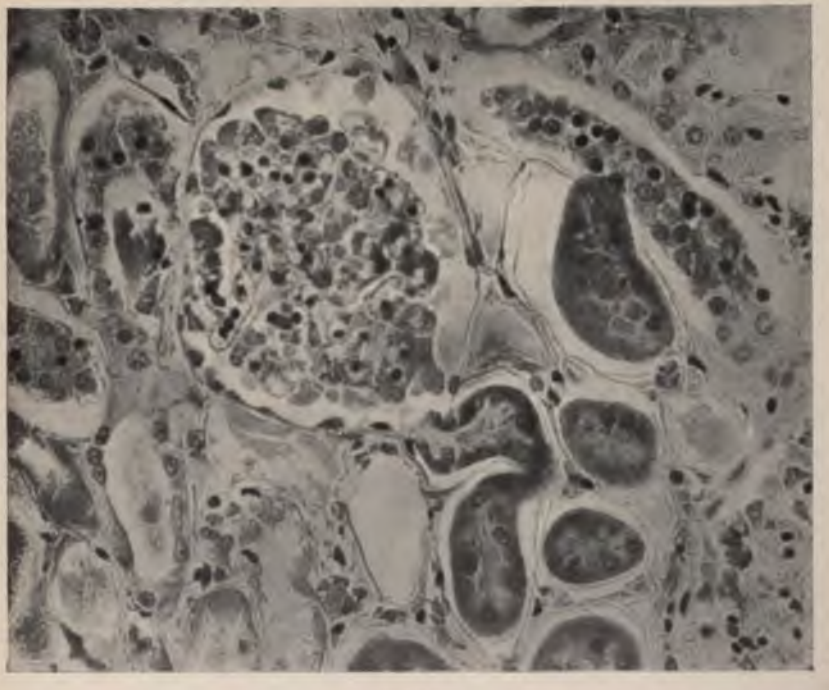


FIG. 8.

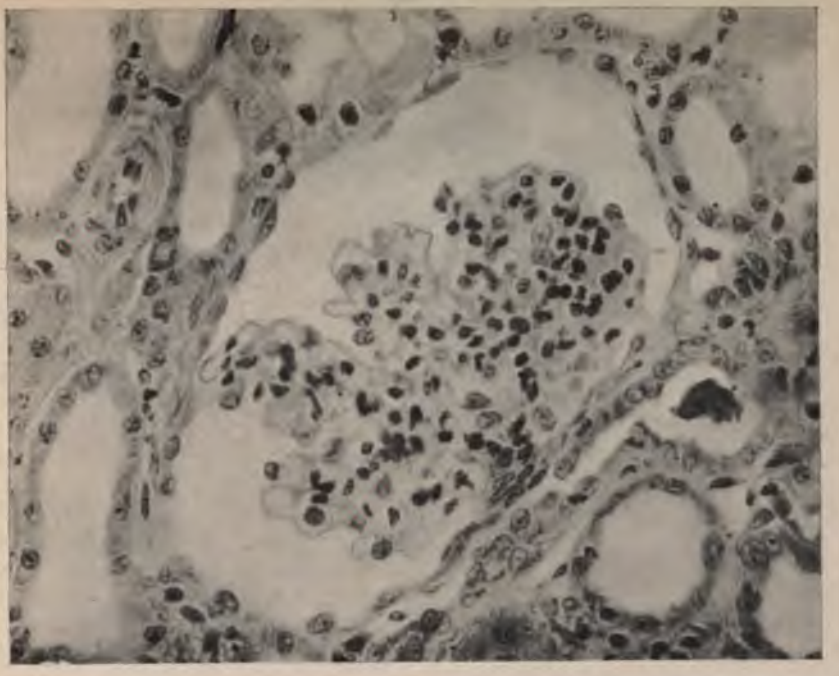


FIG. 9.

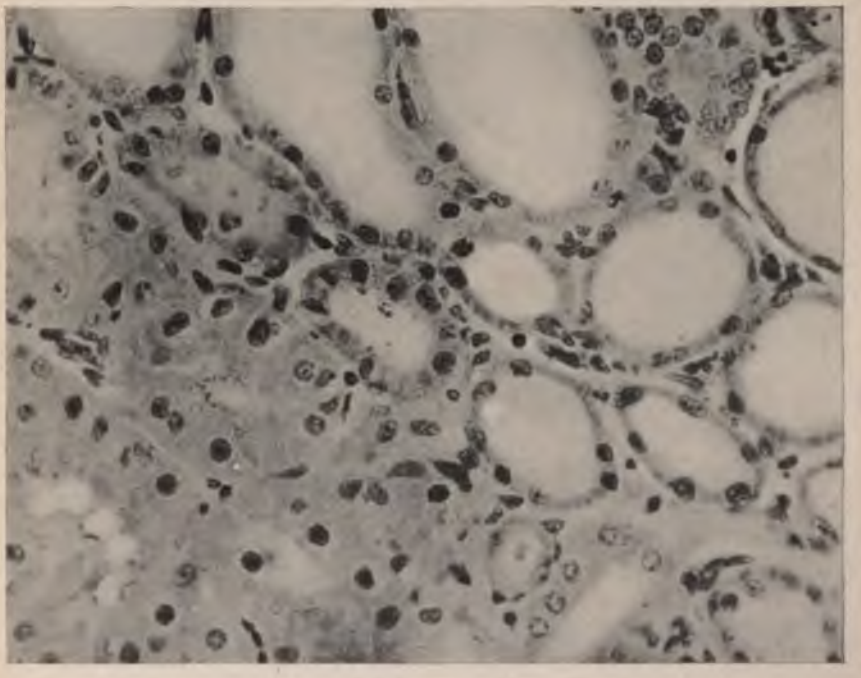


FIG. 10.

Rabbit No. 15. First day. Rabbit caged.

Second day. Urine: no albumin, no casts. Given 5 ccm. of 5% solution of potassium bichromate.

Third day. Urine: albumin, very slight trace. Rare granular cast.

Fourth day. Urine: albumin, very slight trace. Rare granular cast. Given .5 ccm. of 5% solution of potassium bichromate.

Fifth day. Urine: albumin, very slight trace. Rare granular cast.

Sixth day. Urine: albumin, large trace. Very many fine granular casts of various sizes. Few hyaline casts, mostly of large caliber.

Eighth day. Urine: albumin, trace. Many casts, fine and coarse granular, few with cells adherent. Few hyaline casts.

Ninth day. Urine: albumin, slight trace. Many casts, fine and coarse granular, and hyaline. Some cells and fat on casts.

Tenth day. Urine: albumin, large trace. Many casts, hyaline predominating. Animal found dead.

Kidney: Macroscopically, apparently normal. Microscopically, glomeruli apparently normal, though they seem rather cellular. There is necrosis of the cells of the convoluted tubules, especially those close to the capsule. In most cases the lumen is preserved, but filled with granular material. There are many casts, most of them granular, some hyaline.

TRYPAN RED.

The urinalysis of animals which are given injections of trypan red did not show many casts, but the casts had a tendency to appear in showers, great numbers one day and very few the next. A few hyaline casts were seen. The albumin was

not present in large amounts and the animals did not seem sick, so that it was inferred that the experiments might not prove very satisfactory. Study of the kidneys confirmed this to a certain extent. All the tissue appeared very red and the markings were not distinct. On microscopic examination of the kidney sections the most striking thing was the great increase in cellular elements, especially in the glomeruli in the early stages and in the connective tissue in the cases of longer standing. The blood vessels contained a great many red blood corpuscles. There was very little necrosis of any of the tubular epithelium, but in a few places the casts in process of formation could be seen. Some of the cells showed the initial swelling with the loss of cell boundaries and destruction of lumen, and in other places real necrosis was present. Then further along the granular material was seen within the tubule, and finally a well-formed cast.

This experiment may be given as typical of those performed with this substance.

Rabbit No. 19. First day. Animal caged. Given 20 minims trypan red.

Second day. Urine: no albumin, no casts.

Third day. Urine: albumin, slightest possible trace. Rare granular cast.

Fourth day. Urine: albumin, slightest possible trace. Rare granular cast. Given 20 minims trypan red.

Fifth day. Urine: albumin very slight trace. Occasional granular cast.

Tenth day. Urine: albumin, slight trace. Occasional granular cast. Given 20 minims trypan red.

Twelfth day. Urine: albumin, trace. Many granular and occasional hyaline casts.

Fifteenth day. Urine: albumin, very slight trace. Occasional hyaline and fine granular casts.

Seventeenth day. Urine: albumin, very slight trace. Few hyaline and fine granular casts. Given 20 minims trypan red.

Twentieth day. Urine: albumin, very slight trace. Occasional granular and rare hyaline cast.

Thirty-second day. Urine: albumin, very slight trace, no casts. Given 80 minims trypan red.

Thirty-fourth day. Urine: albumin, very slight trace. Rare granular cast.

Thirty-sixth day. Urine: albumin, slightest possible trace. Many fine granular casts.

Thirty-eighth day. Urine: albumin, very slight trace. Occasional granular casts.

Fortieth day. Urine: albumin, very slight trace. Many granular casts. Animal killed.

Kidney: Macroscopically, very dark red, markings not distinct. Microscopically, section is very cellular, especially the connective tissue. The glomeruli contain in addition to the increase in the cellular elements many red blood corpuscles. The tubules are very well preserved, but a few scattered necrotic tubules may be seen. They are almost entirely the convoluted tubules, rarely the straight tubules. Only a very few casts can be found.

ARSENIC.

The experiments with Fowler's solution were also unsatisfactory. Very few casts were found in the urine and the kidney sections revealed little

of interest relative to cast formation. The glomeruli appeared very cellular, but there was only slight necrosis of the tubular epithelium. There was a good deal of blood pigment seen in the sections. This case will illustrate the experiments with arsenic.

Rabbit No. 18. First day. Rabbit caged.

Second day. Urine: no albumin, no casts.

Third day. Urine: no albumin, no casts. Given 1 minim Fowler's solution.

Fourth day. Urine: albumin, slightest possible trace. Rare granular cast. Given 2 minims Fowler's solution.

Fifth day. Urine: albumin, slightest possible trace. No casts.

Sixth day. Urine: albumin, slightest possible trace. Occasional fine granular cast.

Seventh day. Urine: albumin, slightest possible trace. Very rare granular cast. Given 2 minims Fowler's solution.

Eighth day. Urine: albumin, slight trace. No casts. Animal found dead.

Kidney: Microscopically, glomeruli very cellular, filling whole space. Very little necrosis of convoluted tubules and only a small amount of granular detritus. Rarely can any casts be seen. There is a considerable amount of blood pigment free in the tubules.

CANTHARIDIN.

Cantharidin produces lesions in the glomeruli and tubules, but not of the same character as the other irritants. There was very little necrosis of the tubular epithelium and consequently little chance to study cast formation. Many single cells are seen free in the tubules evidently broken

away from the lining epithelium. The whole section is cellular, especially the glomeruli, and the blood vessels are everywhere very distinct. One experiment is cited.

Rabbit No. 29. First day. 600 gm., rabbit caged.

Second day. Urine: albumin, slightest possible trace. No casts. Given .001 gm. cantharidin.

Third day. Urine: albumin, slightest possible trace. No casts.

Fourth day. Urine: albumin, very slight trace. No casts. Given .001 gm. cantharidin.

Fifth day. Urine: albumin, trace. Considerably many casts, fine granular, sometimes with cells adherent, occasionally blood adherent.

Sixth day. Urine: albumin, large trace. Many casts, fine granular and hyaline with cells and blood adherent. Some highly refracting.

Seventh day. Urine: albumin, large trace. Only very rare granular cast. Animal killed.

Kidney: Microscopically, section appears very cellular, and many red blood corpuscles may be seen. The lesion of the convoluted tubules is apparently a desquamative one, for large numbers of cells are free in the tubule, but there is very little necrosis of the cells composing the tubule. Very few casts may be seen.

These experiments with trypan red, arsenic and cantharidin are valuable in this connection, not because they furnish material for study of cast formation, but because they furnish negative evidence in support of the described histogenesis of the process. These animals had albuminuria, but very few casts in the urine, and the kidney sections showed

few casts in the tubules. The lesions only to a very slight extent involved the tubular epithelium, but were largely in the glomeruli and connective tissue. As far as it goes this is in support of the theory that it is from the necrosis and destruction of the tubules and not from albumin excreted through the glomeruli that casts arise. This theory of cast formation is positively supported by the histological evidence adduced in connection with the degenerative lesions of the tubular epithelium and by the results of urine analysis.[4]

CONCLUSIONS.

From these experiments it would seem that the following conclusions may be drawn:

1. It is possible by the injections of uranium nitrate and other irritants to produce in rabbits an albuminuria and cylindruria dependent upon lesions of the kidney simulating nephritis in man.

2. Granular casts are the first to appear in the urine when the kidney is attacked by an irritant.

3. Casts are more common in the urine when the kidney lesion is primarily a necrosis of the tubular epithelium.

4. Casts arise from the degeneration and necrosis of the cells of the tubular epithelium of the kidney. Entire necrotic cells may desquamate and at first remain distinct from one another, then become massed together, and finally formed into a definite plug, taking the shape of the tu-

[4] I wish to express my thanks to Dr. Christian for his constant interest in the experiments, and also for his kind assistance in the preparation of this report.

bule in which it is formed. The same process takes place with cell fragments and granular material derived from disintegrated cells. The casts are all granular at first and later become hyaline as they pass down the tubule in the urinary stream.

DESCRIPTIONS OF PLATES.

FIG. 1. Shows swelling of cells of convoluted tubules, with a loss of cell boundaries and obscuring of lumen.
FIG. 2. Shows necrosis of cells of convoluted tubules and the necrotic mass breaking away.
FIG. 3. Shows necrotic material within tubules, broken or sectional in appearance; few nuclei evident in the mass.
FIG. 4. Casts within tubules, appearing as solid plugs, but showing origin from cells.
FIG. 5. Granular casts within tubules.
FIG. 6. Granular cast within tubule, cell adherent to cast.
FIG. 7. Hyaline casts within normal tubules.
FIG. 8. Apparently normal gomerulus and a normal tubule leading from it.
FIG. 9. Shows a glomerular tuft in a dilated glomerular space.
FIG. 10. Shows dilated tubules in a chronic case.

AGE IN ITS RELATION TO ARTERIOSCLEROSIS AND DEATH FROM ARTERIOSCLEROSIS.

BY WILLIAM H. SMITH, M.D., BOSTON,

Medical House Pupil, Massachusetts General Hospital, 1897; Visiting Physician to the Out-Patient Department of the Massachusetts General Hospital.

(From the Clinico-Pathological Laboratory of the Massachusetts General Hospital.)

Of the two thousand cases coming to autopsy at the Massachusetts General Hospital in the past ten years, 442, or 22.1%, showed more or less arteriosclerosis. Two facts must be considered in regard to this material; first, cases received at this hospital are chiefly acute cases or cases suffering from acute exacerbation. It is in no sense a hospital for chronic disease. Second, post-mortem examination of the head is limited chiefly to those cases with head symptoms. Were it possible to obtain permission for a complete examination of the head in all cases, the number showing arteriosclerosis of the cerebral vessels might be much greater. It may then be said that about one fifth of all cases coming to autopsy at the Massachusetts General Hospital, where acute cases are chiefly admitted and post-mortem examination is somewhat restricted, show more or less arteriosclerosis. In all of these 442 cases the arteriosclerosis was sufficient to warrant it being included in the anatomical diagnosis.[1]

[1] The proportion of males to females admitted to the Massachusetts General Hospital in the last ten years is not quite 3 to 2.

Sex and Nationality,	Male.	Female.	American.	Foreign.	Colored.	?
	329	113	214	187	23	18

In this series of 442 cases arteriosclerosis was nearly three times as common in men as in women, and about equally frequent in Americans and foreigners.

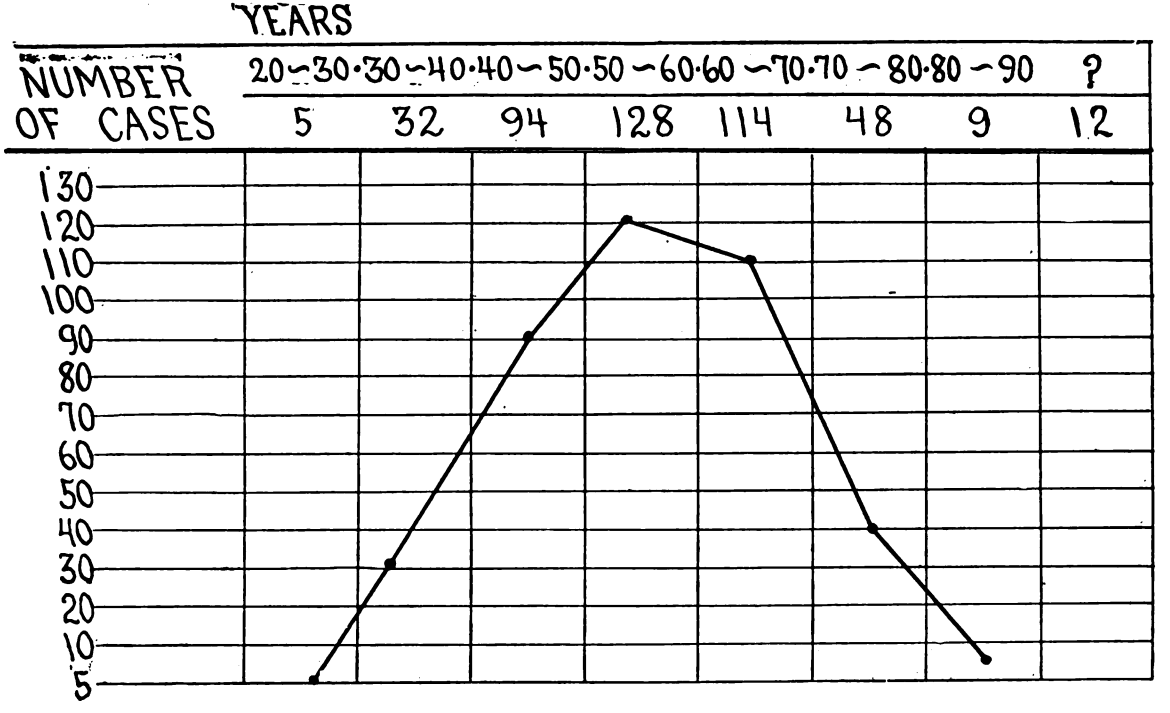
Age.—A glance at Chart 1 will show that in this series the age in approximately one fifth of the cases was between forty and fifty years; in one third between fifty and sixty, and nearly one third between sixty and seventy.

Fifty-nine of these cases gave history of father or mother dying late in life from apoplexy, cardiac or renal disease.

Habits.—There were 135 who used alcohol in moderation; 57 in excess. Nearly 50% of the 442 cases used alcohol to some extent. Syphilis was acknowledged or present in 44 cases, nearly 10%. In 10 cases lead as a predisposing factor had to be considered. In none was gout apparently an antecedent.

Previous illness.—Of the acute infections, rheumatism was recorded in 64, influenza in 42, typhoid in 40, pneumonia in 31, diphtheria in 21, scarlet fever in 15; 73 had had gonorrhea. No definite deductions as to the part acute infections played in the production of arteriosclerosis were attempted. That rheumatism damaged the arteries as well as the heart valves was strongly suggested from the analysis of these cases in several instances. Arteriosclerosis and glomer-

CHART 1.


YEARS
NUMBER OF CASES
20–30 · 30–40 · 40–50 · 50–60 · 60–70 · 70–80 · 80–90 · ?
5 · 32 · 94 · 128 · 114 · 48 · 9 · 12
130
120
110
100
90
80
70
60
50
40
30
20
10
5

ulo-nephritis were associated frequently enough to suggest a common factor in their production.

Deductions.—From a study of these 442 cases, in which arteriosclerosis was present at autopsy, the following facts were ascertained: Arteriosclerosis was three times as common in men as in women, and about as frequent in Americans as foreigners. Two thirds of these cases occurred between fifty and seventy years of age. About the same number between the ages of fifty and sixty, and from sixty to seventy. It is a disease of the fifth decade, as well as of the sixth and seventh decades.

It occurred no earlier in the colored race than those of other nationalities in this series. An inherited, or syphilitic, background was present in 14, and 10% of the cases, while 50% used alcohol.

Fatal cases.—Inasmuch as only a small number of these patients died as a result of their arteriosclerosis, an analysis of the clinical[2] and autopsy records was made to determine how many of them died directly or indirectly from the disease. There were 182 cases. A group of prostatic cases, 22 in number, was omitted, owing to the impossibility of determining what part the arteriosclerosis played in causing death. These were cases of prostatic adenoma, or carcinoma with cystitis, ureteritis, pyelitis, pyelo-nephrosis, hydronephrosis, suppurative and chronic nephritis. In some of these prostatic cases death was due to

[2] I wish to thank Dr. C. L. Overlander for his abstracts of the clinical records.

cardiac or renal disease, in a smaller group to septicemia.

These 182 cases for the purpose of analysis will be considered under four groups:

1. Cardio-renal.
2. Cerebral.
3. Aneurysmal.
4. A, gangrene; B, gangrene with diabetes; C, diabetes alone.

Of the cardio-renal group, there were 124 cases; of the cerebral, 26; of the aneurysmal, 19; of the gangrene, 13.

Careful analysis of the clinical and autopsy records was made in assigning cases to the various groups.

Group 1, Cardio-Renal Group 124 cases.

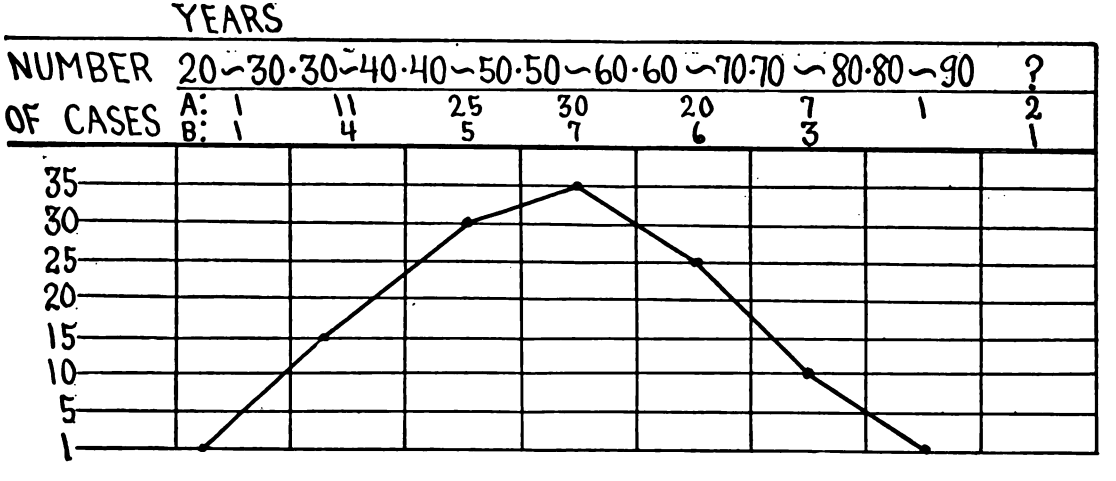
	Male.	Female.	American.	Foreign.	Colored.	?
A,	67	30	47	4	7	3
B,	25	2	15	10	2	
	92	32	62	50	9	3

Just as in the whole series of 442 cases, three times as many men as women had arteriosclerosis, so in the fatal cases this proportion holds. There was no marked difference between those foreign and American.

Age.—The age chart in this cardio-renal group is of interest.

By this chart it will be seen that 37 of the 124 cases died between the ages of fifty and sixty; thirty of the 124 cases died between forty and fifty. In other words, 50% of the cases dying of

CHART 2


YEARS
NUMBER OF CASES
20–30 30–40 40–50 50–60 60–70 70–80 80–90 ?
A: 1 11 25 30 20 7 1 2
B: 1 4 5 7 6 3 1
35
30
25
20
15
10
5
1

cardio-renal manifestation were in the fourth and fifth decades, nearly as many in the fourth decade as in the fifth.

Group 2, Cerebral Group.

Male.	Female.	American.	Foreign.	Colored.	?
20	6	13	9	3	1

Of these 26 cases, 24 had cerebral hemorrhage, two thrombosis. In this group males were three times more affected than females.

The maximum number of deaths occurred between sixty and seventy years in the cerebral group. Nearly as many between fifty and sixty. Nearly one half of the cerebral hemorrhages occurred in the fifth and sixth decades. Whereas the cardio-renal group reached its maximum fatality in the fourth and fifth decades, the cerebral hemorrhage fatality was greatest in the fifth and sixth.

It is interesting in connection with this group to note that in 6 of these cases there was a previous history suggestive of cerebral hemorrhage from three years to six months before the final attack, while in 5 of the cardiac cases in which the brain was examined there was evidence of previous cerebral hemorrhage. In one case in the renal group an apoplectic cyst was found.

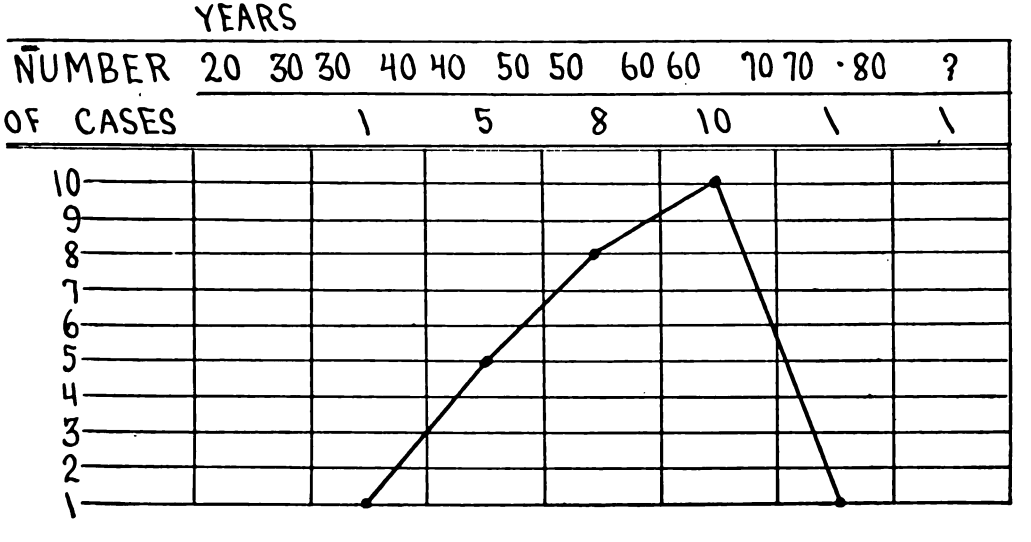
Group 3, Aneurysmal Group.

Male.	Female.	American.	Foreign.	Colored.
19	0	7	11	1

Of these 19 cases, all were males.

The deaths, as may be seen from Chart 4, were

CHART 3.


YEARS
NUMBER OF CASES
20 30
30 40
40 50
50 60
60 70
70 80
?
1
5
8
10
1
1
10
9
8
7
6
5
4
3
2
1

greatest in the third and fourth decades; 15 of the 19 cases died before the age of fifty.

Syphilis was acknowledged in 5 of this group; 5 denying syphilis acknowledged gonorrhea. There were 3 sailors, 3 painters, in this series of 19 cases. In possibly three others their occupation subjected them to prolonged strain. There were 22 aneurysms in this group of 19; 10 of the arch, 5 of the thoracic aorta, 3 of the abdominal aorta, 1 of the innominate, 2 of the right iliac and 1 of the right femoral.

In 14 cases death resulted from rupture of the aneurysm; thrice into the trachea, thrice into the mediastinum, twice each into the left bronchus, pulmonary artery and pericardium, and once each into the retroperitoneal tissues and into the tissue of the thigh. In 7 cases of the cardio-renal group, there was some dilatation of the arch, but not sufficient to be classed as aneurysmal.

Group 4, Gangrene Group.

This group is made up of

A. Gangrene.

B. Gangrene with diabetes.

C. Diabetes.

	Male.	Female.	American.	Foreign.	Colored.	?
A,	5	1	3	2	0	1
B,	1	4	3	1	1	
C,	1	1	2	0	0	
	7	6	8	3	1	1

Ten of the 13 cases included in this group died between the ages of sixty and eighty.

CHART 4.

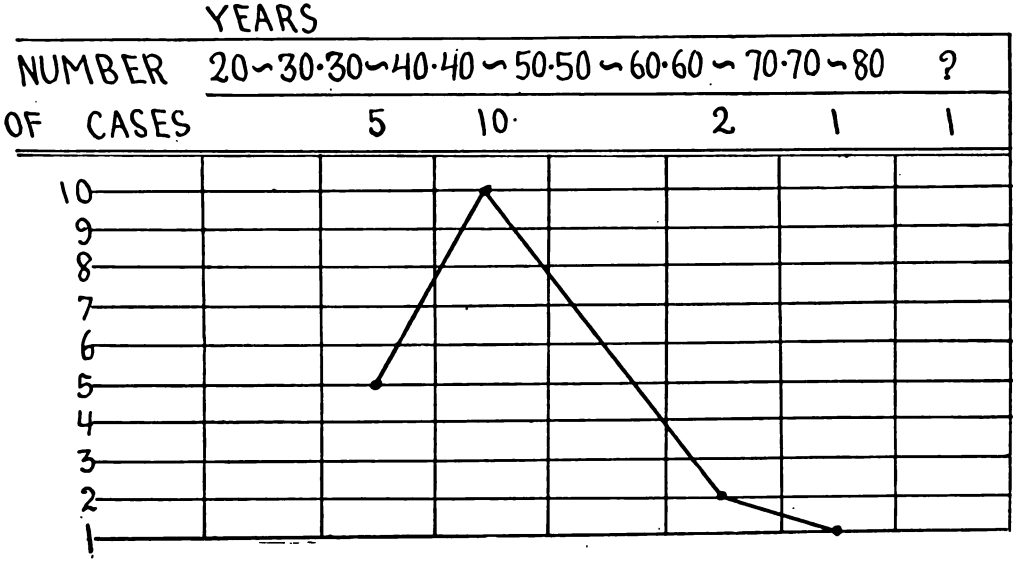
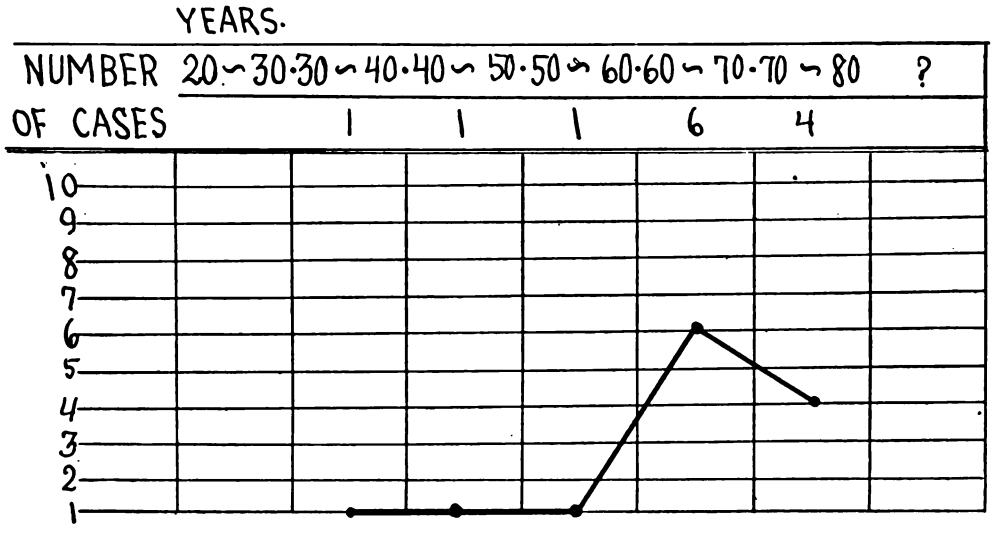

YEARS
NUMBER
20~30
30~40
40~50
50~60
60~70
70~80
?
OF CASES
5
10
2
1
1
10
9
8
7
6
5
4
3
2
1

CHART 5.


YEARS.
NUMBER OF CASES
20 ~ 30 · 30 ~ 40 · 40 ~ 50 · 50 ~ 60 · 60 ~ 70 · 70 ~ 80 ?
1 1 1 6 4
10
9
8
7
6
5
4
3
2
1

Gangrene alone, singly or in combination with diabetes in this arteriosclerosis series, caused death late in life. It occupies the sixth and seventh decades.

The distribution of the gangrene in Group *A* was in the right foot in 3 cases, in the left in 2, in both feet in 1; 5 of the 6 cases required amputation. In 1, with thrombosis of the left popliteal artery, death resulted from coronary thrombosis. In 4 of the 5 operative cases, death was directly due to the arteriosclerotic condition. In the fifth there was a terminal bronchopneumonia, with pneumococcus septicemia.

The distribution of gangrene with diabetes in Group *B* was as follows: right foot in 3 cases, left foot in 1, left hand in 1. Four of these cases died in coma; one post-operative.

The condition of the pancreas was as follows: in one case it was normal, in one there was post-mortem change with no evidence of hyaline degeneration of the islands of Langerhans. In two, these islands showed hyaline degeneration; in one there was also chronic interstitial pancreatitis.

Group C: Diabetes Group.

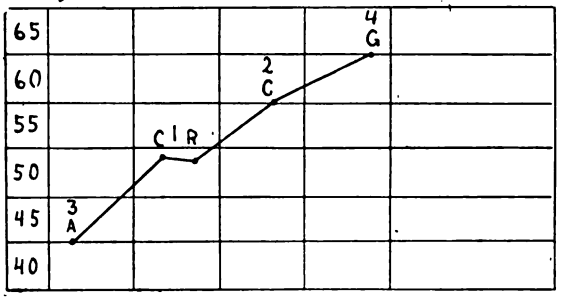
Both patients died in coma; one had in addition terminal streptococcus septicemia.

The pancreas in both of these cases showed some change; in one hypoplasia, with slight chronic interstitial pancreatitis; in the other, slight fatty infiltration with chronic interstitial pancreatitis.

The average age of the patients in these four groups may be seen in the following chart:

CHART 6

AVERAGE AGE OF DEATH IN GROUPS 1,2,3&4.



1. Cardio-renal. 2. Cerebral. 3. Aneurysmal. 4. Gangrene.

CONCLUSIONS.

In this series of 2,000 autopsies, 442 cases, or 22.1%, showed more or less arteriosclerosis.

Arteriosclerosis was three times as common in the male as in the female. It occurred no earlier in the colored race in this series. The average age of the cardio-renal group was nearly fifty-five. The average age of the cerebral group was nearly sixty. Fifty per cent of the cases of cerebral hemorrhage occurred in the fifth and sixth decades and was three times as common in the male as in the female. All the cases of aneurysm were in males. The average age of death was nearly forty-five. Death from gangrene and

diabetes was incident to the last decades,—the sixth and seventh; the average age nearly sixty-five.

I wish to thank the visiting physicians of the Massachusetts General Hospital for permission to use their records, and Dr. James H. Wright for the privilege of access to the autopsy records.

TUBERCULOUS PERITONITIS.

A STUDY OF 122 CASES TREATED AT THE MASSACHUSETTS GENERAL HOSPITAL BETWEEN 1900 AND 1907.

BY ARTHUR K. STONE, M.D., BOSTON,
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TUBERCULOUS peritonitis is a subject about which cluster many unsolved problems, although much has been written since König's second paper in 1892. The swing of the pendulum of opinion has been extreme. First there was the general feeling of hopelessness in regard to the outcome of cases diagnosed as tuberculous peritonitis, and then followed a period of extreme hope for all such as were seen in time to have a surgical operation. Many cases were found to recover. But as more and more operations were done, and men with large clinics were able to follow their results, it was found that all cases were not cured, so that by 1901 Borchgrevink, a Swedish surgeon, took extreme ground against operation, saying that operations were not

United States, Murphy and Mayo and Douglas have urged " aggressive surgery " on the ground that it materially influences the prognosis favorably.

Not only is there division among the writers in regard to operations as a therapeutic procedure but also there are wide differences of opinion as to how the infection is introduced to the peritoneum; whether it comes from the blood, from the passage of the bacilli through the intestinal wall, or from the Fallopian tubes to the peritoneum. The Gynecological Congress at Rome, in 1902, discussed but did not settle these questions.

The operators who believe that surgical interference is an actively remedial therapeutic measure are hopelessly divided as to the reason why a simple incision through the abdominal wall should bring about the destruction of the bacilli of tuberculosis in the tubercles covering the peritoneum. Neither is there any universality in the technic employed by the surgeons to accomplish their results. For the most part such methods, as attempting to disinfect the peritoneal cavity with antiseptics, have been given up as well as that of having the operation take place in the direct sunlight. Most operators advise against trying to separate adhesions of any density. Mayo, however, advocates careful search for the primary focus, in spite of adhesions.

The exudate in cases of tuberculous peritonitis has been considered as a harmful substance which should be removed. Bacilli have sometimes

been found in the fluid, and it has been taken for granted that by means of the fluid the organisms were still more widely disseminated throughout the abdominal cavity. Others have held that the fluid contained toxins, and others have removed it for the discomfort produced, and Mayo would remove it that the ends of the Fallopian tubes might seal up so that the bacilli should not escape into the abdominal cavity from these organs. Gelpke and others advance the theory that the exudate rather contains bactericidal bodies and is an effort of nature to effect a cure and therefore should not be removed or, at least, until such time should have elapsed that would make it probable that the fluid was no longer potent when it should be removed with the hope that a new and more powerful exudate would re-form and the process of cure thus be accelerated.

The question of frequency in sex is in dispute, although it had been supposed that it was settled that women were more prone to be attacked than men.

From this very brief survey of the subject it will be seen that much more will have to be written before the questions of tuberculous peritonitis will be settled.

My personal interest in this subject was aroused by the opportunity which I had, during 1907, to follow for a long period of time several cases of tuberculous peritonitis that had not been operated upon. In these cases I saw patients with

well-marked ascites, after some time, suddenly begin to improve, the fluid to disappear, the patient to take on flesh and strength and to appear perfectly well. In one of these cases there was an opportunity, after the lapse of several months, to inspect the peritoneum, which was opened for an intercurrent disease. At this time it was found that the intestine and omentum were still thickly coated with miliary tubercles. In another case fluid distending the belly quickly disappeared, and the patient (against my advice) was playing golf within four weeks, after a change of residence. This case has since had no return of the ascites.

From these patients it was evident that rapid improvement could take place in the exudative form of tuberculous peritonitis which, had an operation been performed, would have been attributed to the effects of the operation. This led me to a partial review of the literature; and it was clear that since 1900 there was much greater conservatism than formerly among the foreign surgical writers as to the curative value of simple operations. Even the Mayo brothers, though asserting that simple incision and drainage aids recovery in a remarkable way, were evidently dissatisfied with their results and began to substitute mutilating operations in order to obtain still better results. First they did total removal of the uterus, tubes and ovaries, but in their 1905 paper advocate only the removal of the Fallopian tubes. Therefore, we must con-

clude that they, to a degree, are in harmony with the conservative foreign writers.

It must be admitted at the outset by any one who wishes to advocate a conservative line of treatment in tuberculous peritonitis that he must show good and sufficient reason for so doing, as the statistics up to date have, for the most part, shown much better results for the cases treated surgically than for those which have been treated without surgical intervention.

If one stops for a moment to think, there are many reasons why this should have been so in the past. The medical world owes much to Kōnig, in that he first brought forcibly to the attention of the profession the fact that tuberculous peritonitis was a common and also curable condition.[1] Previous to that, the hospital physicians, who have been the teachers, had with few exceptions seen only the last stages of tuberculous peritonitis in their wards. They knew it only as a hopeless condition. Most of the milder cases passed unrecognized by the practitioners, and either got well spontaneously or gradually passed into a hopeless condition, when they sought refuge for their last days under the sheltering roof of some hospital or almshouse. Even of late years the list of so-called medical cases includes a number of rejected surgical cases, — cases where even enthusiastic operators

[1] It is interesting to know that one of the first, if not the first, operation done in this country was performed by Dr. Z. B. Adams, of Framingham, in 1884, the same year as that in which König's first paper appeared. The patient is still alive and well.

have seen that surgical interference would be inadvisable. Medical treatment many times has consisted in simply making a diagnosis, possibly withdrawing the fluid by tapping, and then sending the patients to their homes again, with very general advice as to manner of life, etc. The medical treatment of the future will,I believe, consider the patient with tuberculous peritonitis as seriously as one with incipient tuberculosis of the lungs is now considered, and most careful attention be given to home surroundings and personal hygiene, fresh air, good food, and last but not least, supervision of work or exercise.

To get really valuable statistics will take at least another decade. But when the various plans of state and municipal registration and oversight of tuberculosis, in whatever form it may appear, is carried to its completion we may hope for much more reliable statistics as to the value of the results of our so-called medical measures of cure.

In the meantime, statistics of a series of cases may help to emphasize some of the questions which the operator and the observer must try to answer in order that he may contribute his mite to the solution of this complex problem.

Dr. Frederick C. Shattuck reported in 1902 the cases of tuberculous peritonitis appearing at the Massachusetts General Hospital from 1889 to 1900, 98 in number. I have been over the cases of tuberculous peritonitis from 1900 to October, 1907. I am indebted to the various

members of the staff of the Massachusetts General Hospital for the permission to study their cases.

The total number of cases that I have considered is 122.

Sex. There were 62 males and 60 females. If we deduct the 16 children under 10 years of age, of whom 10 were males and 6 females, we have 52 males and 54 females. That is to say, in a general clinic where men, women and children are treated there was no discrimination as to sex. This coincides with the 28 Boston City Hospital cases reported by Bottomley.

This is very different from some of the statistics furnished from other clinics, as, for example, at the Mayos' clinic there were 4 women to 1 man. This is the most extreme disproportion that I know of as being reported from a general clinic. The large amount of gynecological operating would probably account for the disproportion of 2 women to 1 man which has been the generally accepted ratio in the past.

Age.— As would be expected from our knowledge about tuberculosis no age is exempt, but the third decade of life furnishes the greater number of victims.

Up to five years of age there were 10 cases. Seven of these were males and 3 females. The youngest of these was one year and seven months old and the next youngest two years old, both boys.

From six to ten years of age there were 6 cases, 3 males and 3 females.

From eleven to twenty years of age there were 34 cases; of these 21 were males and 13 females. Two females and one male were married.

From twenty-one to thirty years of age there were 48 cases. Of these 21 were males and 29 were females, of whom 9 were married, and 20 were single. Of the men 6 were married.

From thirty-one to forty-five years of age there were 17 cases, of whom 5 were males and 12 were females. All of the males had been married, and 10 of the females had been married.

From forty-six years old and upward there were 4 cases, all men, the oldest of whom was seventy-three years of age. In these cases all were married.

Color.—There were 8 colored patients among the 122 cases.

In the out-patient department during the past two years, 1906–1907, there have been 1,038 cases of tuberculosis reported, and of these 33 have been colored persons. The percentage has therefore been about twice as great as would have been expected from the general proportion of colored patients having tuberculosis that come to the general clinic.

Operative and Non-Operative Cases.

Cases treated surgically,	71:	Males, 34;	Females, 37.
Cases treated without operation,	51:	Males, 28;	Females, 23.

Of the 71 operative cases 38 were transferred from the medical wards, where they entered, to

the surgical wards. In a few instances, cases that entered as surgical patients were sent to the medical wards as being unfit for operation. In a number of cases the surgeons, though called in consultation, declined to operate.

Mortality.— Of the 122 cases 10 died in the hospital, about 8%. Six cases died in the medical wards, and the autopsies showed:

1. Mitral disease of the heart, as well as tuberculosis of the upper lobe of the left lung in addi tion to the peritonitis. The patient was apparently doing well, when the heart suddenly gave out.

2. General miliary tuberculosis of the lungs and hemorrhage from the bowel.

3. Died of perforation of the bowel. A child very sick on admission.

4. Died in ten days after entry. Great emaciation, *purpura*. Tuberculous ulcers about cecum. Old foci at apices.

5. General cachexia, — tuberculosis of the lungs with cavities.

6. General decline, with persistent diarrhea. Tuberculous ulcers were found in large intestine. An old focus was found at the left apex, and mesenteric glands enlarged.

None of these patients could be considered for surgical treatment when seen at the hospital; the diseased condition had advanced so far that death was the only possible outcome.

The four surgical cases died under the following conditions:

1. The patient became septic, the wound

breaking down and discharging foul pus. Purulent peritonitis had been found at the operation. The patient had been attacked suddenly seven weeks before entrance to the hospital.

2. There was a general increase of pain and tenderness and an outbreak of purpura. Purulent peritonitis was found at the operation. The symptoms had existed for about one month.

3. The wounds broke down and patient became generally septic. The abdominal cavity could not be entered so dense were the adhesions. Symptoms had developed within six weeks.

4. Abscess resulting in a fecal fistula developed after the operation. Much clear fluid had been found and many adhesions. Several cheesy nodules were removed from the large intestine; there was also a general distribution of tubercles. The symptoms had appeared suddenly only twelve days before.

The previous histories of these cases made the findings unexpected, though when found the result was obvious.

Subsequent history. — So far as the after histories of the patients have been followed it has been found that of the 112 who left the hospital alive 27 have since died.[2]

Of these 12 were treated without operation, 15 with operation.

The duration of life in the 15 surgical cases was as follows:

[2] Since the above was written two medical patients were reported to have died soon after leaving the hospital.

1 month or less,	3
1–2 months,	2
3 months,	3
7–8 months.	1
8–10 months,	2
1–2 years,	2

One lived five or six years, had married, and died of some sudden cerebral condition. One lived five years and died of phthisis at the end of that time.

The duration of life in the medical cases was as follows:

1 month or less,	2	both *in extremis*, when taken from the hospital,
1–2 months,	3	two apparently favorable (both refused operation, and one of phthisis.
4 months,	2	
5–6 months,	3	one of whom was operated upon one month later in Colorado: one died of phthisis.
8 months,	1	
2 years+,	1	died of "cough."

It has been possible to find out about the present (February, 1908) condition of 28 living patients, 25%, or one quarter of those leaving the hospital alive. There are undoubtedly others as 28 letters remain unanswered while 19 letters have been returned as undelivered.

Of the 28 who have reported as being alive, surgical cases numbered 17, medical cases numbered 11.[3]

Of the 11 medical cases 6 have been out between one and two years (many of these nearly

[3] Since the above was written 1 medical case has reported herself alive and well, 7 years after discharge.

two years), one between three and four, 1 over five years, 2 over six years; 1 over seven years.

With two exceptions all report themselves in good health. One of these has had a pleuritic exudate in the left chest which has since disappeared. The other is reported as a slim, pale child, though complaining of nothing. One patient who was tapped and had masses in the abdomen after a period of nearly two years writes: " A more healthy, robust girl never lived than I am at the present time."

Of the 17 surgical cases, those reporting themselves, have been out of the hospital as follows:

Under 1 year,	2
1–2 years,	2
More than 2 years,	4
" " 3 "	3
" " 4 "	3
" " 6 "	3

One patient has returned to Ireland and though well has not worked since the operation, over three years ago.

One has a cough and is out each day; the wound still discharges (nearly three years).

One reports in fair condition but has loss of weight and night sweats if she overworks.

One (of a year's standing) is stronger and gaining; the wound still discharges.

One of only a few months' standing feels well, but belly is tender.

In addition to these there are ten others who have been heard from since leaving the hospital, but have not replied to recent letters.

One heard from four months after leaving the hospital. Perfectly well. Little discharge from the scar.

Seven patients were heard from one year after leaving the hospital. One patient had gained 20 lb. No abdominal pain. Had a cough and expectoration.

One reported poor health with pains in lungs and back.

One had been very sick for twelve weeks in another hospital, but was in good condition.

One reported wound broken down and discharging.

One had gained 18lb., felt well and was in Ireland.

One reported her general condition excellent Six months later she was operated for cystitis; no bacilli of tuberculosis found in the urine.

One has had no trouble since operation.

One, four years after the operation, came for distress in stomach to the out-patient department. Nothing was found on examination. Patient was in good physical condition.

One patient came to the out-patient department for headaches and vertigo, four years after the operation.

The last two cases belong in the *cured* class.

Of the seven cases reporting at the end of a year two were evidently in poor condition and one other had a cough and expectoration, nevertheless in good condition.

To recapitulate: Of the 122 cases treated there were in February, 1908:

Dead,	39
Alive, 1908,	29
Heard from, but not in 1908,	10
Letters returned,	19
Not answered,	25
Total,	122

Of the 44 of whom there has been no report whatsoever, the conditions at discharge make it very probable that in a number there has been a fatal ending.

It is specially unfortunate that 25 letters should remain unanswered, as this large number would have made the statistics so much more valuable.

The family history.— In 10 cases only was there any account of tuberculosis in the family, and in but 5 of these cases there was exposure to cases of phthisis possible, while the other 5 were not exposed to family contagion.

The previous history.— Those who reported themselves as being well up to the time of the present illness were 42 in number.

Those who had been sick with other conditions previously to the present attack were 63 in number.

There were 6 cases in which there had been typhoid fever, and in 4 of these, at least, it was reasonable to suppose that the fever had been rather a tubercular fever. Likewise, some of 4 cases of malaria were of doubtful character.

Grippe was spoken of 6 times.

Diarrhea is mentioned as a symptom in 32

cases, and of these 8 had had this symptom for over one year. Six more had had diarrhea for at least a month before entrance.

In 74 there had been no diarrhea, and 9 of these stated that they were usually constipated.

In the remaining 16 cases no mention of the bowel condition is made.

Hemeter in his report of autopsies on 56 cases of tuberculous enteritis states that in but 2 was there tuberculous peritonitis present.

In the two cases above mentioned when ulcerations were found at autopsy in the intestines there was not a general tuberculous peritonitis present, although other foci of tuberculosis were found in the body. Also in a patient of my own where there was very extensive tuberculous enteritis there was no general deposit of tubercles upon the peritoneum.

In spite of the fact that there was diarrhea present in about one quarter of the cases, it does not seem probable that tuberculous enteritis is an important factor in the production of general tuberculous peritonitis.

Ascites was present in two cases, eight and six years previously, and " peritonitis " once at the age of six months.

Pleurisy was spoken of in 4 cases.

Whooping cough was mentioned 10 times, and in several instances, long duration is mentioned.

In 2 instances a miscarriage was attributed as the starting point.

One patient was brought to the hospital septic, in the second week after parturition. The peritonitis was found to be due to a tuberculous process.

The *sputum* was examined for the presence of the bacilli of tuberculosis in 24 cases, sometimes repeatedly. The bacilli of tuberculosis were found in but 3 of these cases.

The *stools* were likewise examined seven times, all with negative results.

Leucocytosis.—The white count was 10,000 or less in 58 cases. It was between 10,000 and 14,000 in 21 cases; it was 14,000 in 2 cases; 15,000 in 3 cases, 16,000 in 2 cases, 17,000 in one case, 18,000 in 2 cases, 20,000 in 1 case, 21,000 in 1 case, 22,000 in 2 cases, and in 1 each 27,000, 28,000 and 40,000.

The patient with a 40,000 white count had no fluid, but tuberculous ulcerations in the large intestine and probable secondary infection. The patient with 28,000 had an abscess rapidly develop which brought her to operation; probably a mixed infection. The case with 27,000 had an acute attack of vomiting and diarrhea for several days before the belly had swollen, and is one of the few cases of acute accumulation of fluid which would bear out Murphy's statement that a high leucocyte count is usual in tuberculous peritonitis. One of the 22,000 cases had little fluid but considerable tenderness about the tubes. The other case was that of two weeks' standing and there

was blood in the stools. The case of 21,000 developed with a chill and the right tube was filled with foul pus; again a secondary infection. The same is true of case with 20,000. Foul pus was also found in one case with 18,000; the other was a child where there was rapid development. The case of 17,000 was one of five months' standing and with probably a general miliary tuberculosis. One of the cases with 16,000 entered the surgical wards with chill and pain in the appendix region, and the other was a case that had been operated upon elsewhere, but had a rapid re-accumulation of free fluid.

Thus, for the most part, the high leucocyte count is accounted for by the presence of septic infection, and, on the whole, the leucocytosis corresponds with the general rule for tuberculosis, namely, a low count.

Onset of symptoms. — There seems to be a general feeling that the symptoms leading to the presence of peritoneal tuberculosis are of an insidious character. The invasion may be unheralded though extensive, but the open outbreak is often sudden and stormy. Gelpke in his recent article states this, though in a note he says that he and others have found that one quarter to one third begin acutely. This coincides with the cases here reported, 36, or 29%, developing suddenly. Bottomley found 13 in his group of 28 cases began acutely, and F. C. Shattuck found 29 of his 98 cases.

Acute symptoms appeared both in the cases

where fluid was present and where it was absent. In the latter class the symptoms were frequently so acute as to simulate appendicitis, i. e., sudden pain and tenderness localized in the right iliac region, usually accompanied with vomiting. Other cases simulated acute inflammation of the Fallopian tubes. The most interesting group was that where the attack was sharp, with abdominal pain or cramps usually accompanied with vomiting, and within a few days the abdomen became tense with fluid.

A typical account is this: the patient had felt tired for a month, then had a sudden attack of pain and the abdomen three days later was distended. In another there was a sudden pain coming on before breakfast. She was weak and feverish for three days, having a little cough and at the end of that time the belly was found swollen.

Another patient that I had the opportunity to see a few days ago had had pleurisy five years ago, and, five days before I saw her, the belly began to swell and when seen it was distended and tense.

The fact that fluid can accumulate suddenly is not emphasized to any extent, but it certainly should be borne in mind.

In several cases that have been under my observation the converse has been true and fluid has been seen to disappear rapidly, but not so rapidly as it has been said to accumulate. In 2 of the cases who reported themselves as being

well, both state that they got worse after leaving the hospital when one "took up Christian Science" and another was given "a medicine," and within a couple of weeks' time the fluid had disappeared in each case and they were able to be about again. A third went to his doctor in New York State and was quickly cured. The presence of acute symptoms, therefore, does not militate against the diagnosis of tuberculosis of the peritoneum, and sudden improvement is not rare.

Tubercles.— The extensive distribution of tubercles in most of the cases that were operated upon demonstrated that the disease has been in progress for some time. Two of the cases specially show this; in one, tuberculous peritonitis was unsuspected, but found in the course of an operation for hernia; the other, a longshoreman who fell into the hold of a vessel and who, when operated upon for what was supposed to be the result of his injuries, was found to have extensive tuberculous peritonitis. Neither of these patients had symptoms pointing to this disease. A young girl who was operated upon for appendicitis, having had tuberculous ascites six months before, was found to have her "intestines swathed in tubercles," yet she had been in apparently perfect health for over four months.

These cases go to show that the processes may be present and give no symptom, but that variations in the patient's physical condition may call forth the exudate.

The peritoneum may have a perfectly typical appearance of tuberculous peritonitis, being everywhere studded with miliary tubercles and have either no fluid at all or have it present in large amounts, and this fluid can accumulate rapidly and also disappear rapidly. All this points to the fact that the ascites is not a symptom to be met with the knife without some special indication for so doing.

Masses.— Indefinite masses were felt in the abdomen in 21 of the cases. This does not include enlarged tubes that were felt by the vagina. These latter were, however, mentioned but three times. The irregular-shaped masses were several times discovered after tapping, and when an operation was performed, were usually found to be rolled up omentum and intestines. Sometimes a very great amount of adherent bowel was found which had given no evidence of its existence from the outside, neither had there been any history of abdominal pain.

Pleuritic effusion.— Evidence of fluid in the chest was found in 19, or 15%, of the cases. In one case there was fluid in both sides of the chest and in the abdomen. A year later, after apparent recovery, fluid reappeared in the left side of the chest, but disappeared again within a few weeks. In another case, mentioned before, but not included in this group of 122 cases, there had been pleurisy with effusion five years before the belly had been attacked.

Fluid in the chest is of no uncommon occur-

rence, but appears to have no bearing on the prognosis of the case.

Signs of phthisis.— Modification of the normal respiratory signs, all the way from harsh breathing with prolonged expiration to well-marked signs of pleurisy or consolidation, were found 59 times, or 48%, of the 122 cases; that is, abnormalities could be found in the course of the examination of the chest in nearly one half of the cases.

Tuberculin. — The tuberculin reaction was tried in 31 cases; 5 did not react, and in 2 the reaction was of doubtful character, and in one no report was made. Two of the five not reacting were proved to have extensive tuberculous peritonitis at operation. The others were unoperated upon. The tests were usually made by the injection of a single dose of the old tuberculin.

Surgical cases.— In 19 of the 71 surgical cases nothing more was done than to wash out the peritoneal cavity as far as possible with salt solution or to wipe it dry with gauze sponges. In ten more of the cases nothing whatever was attempted more than to look into the abdominal cavity, and then to close the wound again. Adhesions at times prevented the cavity from being opened.

In 4 cases the adhesions were broken up as far as possible.

In 6 cases abscesses or distinct foci of cheesy material were removed. One of these was an external abscess with a deep sinus. In one there

was a single broken down retroperitoneal gland, and one presented multiple pus pockets among the adherent intestines.

In 5 cases the appendix was removed. In 3 of these there were no tubercles seen on the appendix itself, though there were many in the peritoneal cavity. In another case there was a section of tuberculous gut found while searching for the appendix which was also removed, no mention being made as to its condition. In the fifth case the tip of the appendix was thickened and filled with pus, and on the surface there were a few ulcers. The ascending and transverse colon were also thickened, and the description reads like a case of cecal tuberculosis with involvement of the appendix, rather than a general diffuse tuberculous peritonitis.

In some of the other cases the condition of the appendix was noted as being not abnormal or else tied up in dense adhesions. Nevertheless, only 5 were removed and of those only 1 could be taken as the starting point of the infection and that was not a general infection. In 1 other case where a sinus had persisted after an appendectomy, the secondary operation disclosed a tuberculous lesion at the bottom of the sinus. But here again there was no diffuse process.

Tubes and ovaries. — In 14 cases Fallopian tubes were removed, 11 times both tubes being removed, and in 3 cases only one tube was removed. In 4 cases the ovaries were also excised

at the same time. The tubes were many times found filled with pus, in some with cheesy débris. In one case where the tubes were practically converted into a cheesy abscess and pus was oozing into the peritoneum, no other tubercles were reported than those in the wall of the tube. In other cases, the interior of the tube was not involved at all although the peritoneal surface was studded with tubercles as was the rest of the peritoneum. There was no case where the condition in any way could be said to be fairly described as a "lupus" of the mucosa.

The tubes may be a source of infection, but it cannot be said that they are the most common source. Rather than any routine removal of the tubes a much more consistent course seems to be to carefully inspect the tubes, and unless specially involved to return them unharmed to their places. In one case where this was done, and although there had been some sharp attacks which would lead one to suppose the tubes were diseased, and the inspection showed that the tubes were somewhat thickened, the patient nevertheless recovered and has remained well and has had no return of discomfort at the menstrual periods which have been regular.

Fluid in the abdominal cavity. — Fluid was reported as present in 84 cases, or nearly 69%. This was demonstrated by operation and tapping 57 times. And also in 22 cases there were undoubted signs of fluid, as shifting dullness, fluid wave, many of the cases having also a dis-

tended abdomen and protruding navel. In 5 other cases there was but little fluid and possibly some doubt as to its presence.

In 35 cases there was no fluid to be made out by the physical signs (except in two cases where doubtful wave or shifting dullness has been found). This was verified 23 times by operation and once at autopsy.

In the remaining 3 cases there was no record made, or else no definite statement as to the presence or absence of fluid. These are to be included probably among the dry cases, as any amount of fluid would probably have been recognized and recorded.

The amount of the ascites fluid varied from a comparatively few ounces to "several gallons"—10 qt., 8 qt., 10 pt. One patient had 10 qt. withdrawn, again over 8 qt. and 10 qt. more were found at the operation, and a certain amount reappeared after the operation. This patient lived five or six years after the operation. With very few exceptions the fluid found was noted as either clear or yellow, or straw colored. It was reported as purulent 3 times, as cloudy once, as dark once, as bloody once, and in another case blood came towards the end of the tapping when previously it had been clear.

By most authorities the dry cases are supposed to be the least favorable as to prognosis, yet 4 only, or 11%, out of the 35 "dry" cases are on the list of those reported as dead. This makes the deaths among the 84 cases with ascites 33, or 39%.

Nineteen of the "dry" cases are among those reported living in February, 1908; 13 of these being of the operative cases.

Three more of the "dry" cases heard from at the end of a year, 2 in excellent condition, 1 in poor health and with a cough. These are also operative cases. Three others reporting after the lapse of a year were medical cases. The other 12 cases have not been heard from. In the operative cases the tubes were removed 6 times; twice the appendix was removed, once as being tubercular, the other being chronic appendicitis with tuberculous nodules on the rest of the peritoneum. Twice the operation was for exploration of a sinus and once the draining of a retroperitoneal gland. One other case might be included here when at the first stay at the hospital there was much fluid present, but eight months later when operated upon for an appendicitis there was no fluid in the belly. In the 23 operative "dry" cases there was general tuberculosis of the peritoneum 16 times, and once of the intestine. Certainly this group of cases makes it seem as though the "dry" cases were rather favorable than otherwise. The question naturally arises, What is a "dry" case? or, in other words, may not many of the cases have passed through the active stage like the last patient whom I have mentioned, and become in the process of healing a "dry" case with only the scars and degenerations of the tuberculous process left behind, to be found by the operator? The

data for the solution of these questions is not at hand.

Tubercles.— Tubercles were found present more or less generally distributed over the parietes, and the peritoneum covering the intestines and pelvic organs in 56, or 78%, of the surgical cases. Of the remainder, in one septic case no note is made. In one case the tubes were mentioned as alone having tubercles and within, the tube was practically a cheesy abscess. In one case the only tuberculous lesion mentioned was the four inches of intestine which was resected. In a number of cases the presence of general distribution of tubercles was not mentioned. Several times the attempt to open the abdomen was futile on account of the dense adhesions, and at others only a pocket was opened, and the general cavity could not be explored.

Adhesions. — In the 71 cases in which the abdomen was examined adhesions were found 54 times while 17 times no mention is made in the records, though from the context their presence may be inferred in at least 3 of these 17 cases. Five of the 17 cases are among those from whom reports have been received. One was the hernia case that had no symptoms of peritonitis and was accidentally discovered and was well when last reported, over four years after the operation. One, also of four years' standing, had both ovaries and tubes and also the appendix removed, and the general tuberculous infection was very extensive. The next case was one in which 4

in. of gut was excised, and was reported in good condition a year later. A fourth case was one where the abdomen was opened and closed, large-sized tubercles being seen. Still another was one in which a tuberculous sinus persisted in the scar after an operation for appendicitis, and the bowels were found studded with tubercles. One case of seven years' standing had no adhesions. Only one case without adhesions is among the list of dead.

On the other hand, among the patients reporting themselves alive at the time of writing, one, where over four years have passed since the operation, had the intestines bound up into a mass and the pelvis walled off so that the ovaries and tubes were not seen by the operator. A patient, reporting herself in good health, had a tumor which turned out to be a "wab of intestine"; in another, reporting likewise, the intestines were matted together, and still in another of nearly seven years' recovery the intestines were firmly matted together. One case reporting nearly three years after the operation had the intestines and omentum adherent to the pelvic organs.

These are taken as examples of cases with extensive adhesions that have remained well over considerable periods of time and showing that such adhesions may exist without any marked hindrance to general comfort and well being.

Menstruation. — Notes regarding menstrua-

tion were recorded in the histories of 36 of the women. It was noted as usually regular in 29 cases; irregular in 5, and absent for a space of nine to thirteen months in 2 cases. Several other cases had not menstruated for two or three months before coming under observation. Nine patients had pain at the time of the catamenia and 9 had no dysmenorrhea. In 13 the amount of blood lost was excessive. Three cases out of the 36 had evidently severe disturbance at the time of the menstrual period.

Of the women of whose after history we have any knowledge 8 have reported in regard to their menstruation, and of 4 others inference may be made, two, speaking of themselves in perfect health and two others having been at the out-patient department several times with no record as to dysmenorrhea. One patient, having the ovaries and tubes removed, reported regular catamenia for six months which then stopped; while another, in like condition, reports that she is "all right monthly." One patient where the tubes were covered with tubercles and thickened but were not removed reports her "periods all right." Three only have dysmenorrhea, one, "some pain before catamenia," one, pain and profuse flow one month, the next, normal, and the other, "painful but not much."

Reaccumulation of fluid.—The reappearance of the ascitic exudate after operation is frequent, and according to some surgeons considered practically universal. Gelpke is inclined to ascribe

to such a reaccumulation the real advantage that may be hoped for by simple operation, on the ground that the new fluid contains active bactericidal properties which make for cure.

Large accumulations do occur after operation, as was seen in one of this series of cases where the patient had been operated upon in Naples, and had had to be tapped two months later and was operated upon a second time having the abdomen again distended with fluid.

Among the operative cases 13 are noted as having a reaccumulation, 18%, a rather small number as compared with the observations of others.

Four cases are recorded as having a large amount reaccumulate, of two small amounts were noted and of the remainder the re-formed exudate probably was not large.

Accidents. — In 3 cases accidents were recorded as taking place during the operation. In one case the cecum which was thickened and tied down by adhesions was opened by the exploring finger. An anastomosis of the intestines was immediately done. There was general tuberculosis of the intestine and peritoneum, and bacilli of tuberculosis were found in the sputum. A letter was returned unopened a year after the operation. Another case where there were dense adhesions, and the ovaries and tubes were removed, the small intestine was torn into in the course of the operation. This patient, though not answering the circular letter recently sent out, was

alive five years after the operation. The third patient had pain in the region of the appendix, and as the coils of intestines were being pushed aside, one of them ruptured. Four inches of tuberculous gut were resected. This patient, though she had a hard and prolonged recovery, with abscesses and sinuses, was reported at the end of a year in "splendid condition." No report has since been obtained.

Sepsis, abscess and sinus formation after operation. — There are reports of general sepsis, breaking down of wounds, with the formation of sinuses and, in a few instances, of fecal fistulæ, in no less than 19 cases, or 26.7% of those cases operated upon. Four of these cases died while still in the hospital with diffuse sepsis. In 3 of the 4 cases the wounds broke down before death, and in one there was an outbreak of purpura. Deducting these desperate cases from the above 19 cases leaves 15, or 21% of the cases who survived the operation who have had sinuses develop after the operation. In 2 of the cases a fecal fistula formed. In a few cases the sinuses closed before leaving the hospital; others report discharge from the sinus for four months, six months, a year, and one case had a discharging wound for two years, which finally closed after going to Colorado. Still another reports a discharging sinus nearly three years after the operation. In two cases abscess and sinuses did not appear till after leaving the hospital.

In only a few instances is there record of the

use of any drainage after the operation. The wounds after a varying length of time simply broke down with a resulting sinus. Defect in the catgut is ascribed in one case, but in the light of the general frequency of such results it seems hardly fair to accuse the catgut, especially as the resulting sinus lasted for two years.

To the advocate of operation the danger of a breakdown of the wounds with a sinus and possibly a fistula must be taken into consideration. It has been supposed by some surgeons that the frequency of sinuses after operation for tuberculous peritonitis was confined to the operations of the last century, but the above figures show that the percentage is still high and that operation, even exploratory operation, cannot be advised with the same freedom that is possible in most other abdominal conditions.

Pathological reports. — Pathological reports are found in 38 of the 71 operative cases, or 50%. With two exceptions tuberculosis was demonstrated. In one of these cases where many tubercles were present,the piece removed for examination showed only thickened and hypertrophied tissue. It is evident that no real tubercle was sent to the pathologist. In another case the appendix alone was sent, and this showed no tuberculosis, although there were many tubercles on both the parietal and visceral peritoneum and also on the omentum.

Whenever the tubercles were examined microscopically the typical changes due to tuber-

culosis were found. The examination of the ordinary macroscopic tubercles in almost every recorded instance, not only here, but in other clinics, gives proof of tuberculosis, and only rarely do cases of pseudo-tuberculosis occur as in the case recently reported by Farrar Cobb, where foreign bodies were found within the tubercles. Cobb, however, makes it plain that pseudo-tuberculosis of the peritoneum is frequent enough to make it practically necessary to clinch the diagnosis in every case with a microscopic examination.

In one case when the microscopic examination showed the typical tubercles the exudate injected into a guinea pig did not kill it. In only a single case were the bacilli of tuberculosis demonstrated in the tubercles.

CONCLUSIONS.

This series of cases presents a number of interesting points.

First, being a general clinic, and drawing from a large and mixed population, the fact that the males and females were in about equal numbers is significant, and is probably nearer to the truth than the figures furnished from the more special clinics.

Second, the onset of symptoms is often sudden and stormy, both in the cases where there is ascitic fluid present and where it is absent.

Third, fluid can go quickly, and improvement take place very rapidly both with and without an operation.

Fourth, tuberculous peritonitis can be latent, unsuspected, so far as symptoms are concerned, and it can remain apparently unchanged for months after active symptoms have subsided and the patient returned to apparent health.

Fifth, foci for the infection of the general peritoneum have not been found in the Fallopian tubes or in the vermiform appendix in this group of cases.

Sixth, operation should only be undertaken when there is some distinct indication; in the cases with fluid exudate, unless there is distress from the distention, it is better to wait for a period with the patient at rest and under the same hygienic conditions to which any case of pulmonary tuberculosis would naturally be subjected, namely, rest, fresh air, good food and, later, moderate regulated exercise. If after six to eight weeks there is no improvement in the symptoms operation should be considered.

Seventh, the patients, when once the disease is arrested, whether by operation or hygienic methods of treatment, must be taught to regulate their lives with the same care that they would had the disease been located in the lungs.

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ON THE EARLY DIASTOLIC HEART SOUND (THE SO-CALLED THIRD HEART SOUND).

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If one place the hand in the region of the cardiac apex of a young individual with a chest wall not too thick, the systolic impulse of the heart is easily palpable. A slight shock may also be felt at the time of closure of the aortic valves. On auscultation one hears the two heart sounds; the first, more prolonged and low pitched but with a clearly defined ending; the second, short, definite, high pitched, clean cut. In the long pause between the close of the aortic valves and the beginning of the next systole, there is often silence. This, however, is not always the case. As I have already pointed out in another communication,[1] a third sound is not infrequently audible, especially in young people with thin chest walls. The sound is softer and of lower pitch than the second sound; sometimes it is a dull, distant thud; sometimes merely a hum; it occurs shortly after the second sound, that is, at the beginning of the long pause. It is, however, always appreciable at a time later than that occupied by a true reduplication of the second sound, and it is audible only or with greatest intensity at or near the apex. In some

cases it may be heard over the lower part of the right ventricle. At times, the sound is followed by the faintest suggestion of an echo resembling a slight, early mitral diastolic murmur. This resemblance has, in some cases, been sufficiently striking to suggest that the phenomenon might be due to a similar mechanical cause; so much so, indeed, that I have long been in the habit of maintaining that the entrance of blood from auricle into ventricle is associated in some instances with a slightly audible sound. This early diastolic sound may be associated with a shock which is just perceptible to the palpating hand. The condition is rendered more readily appreciable, and may be brought out in cases in which it is not otherwise audible by a simple manœuvre. If the patient turn well upon the left side in such a position that the chest overhangs the edge of the bed, the apex impulse of the heart which is thrown more directly against the chest wall, becomes more forcible and may be more easily studied by the hand and the stethoscope. On palpation of a heart in this position it is not very uncommon to feel, first, the systolic impulse, then a slight suggestion of the shock accompanying the closure of the aortic valves and second sound, and then, with the relaxation of the ventricle, a third impulse following rather closely after the second sound. In some cases in which an impulse is palpable auscultation reveals no actual well-defined sound. One is, however, sensible of a slight shock to the tympanic

membrane analogous to that which is felt with the palpating hand. The sound and shock may be more appreciable at the end of expiration.

This sound is certainly not an abnormal phenomenon. It has been familiar to me for over twenty years, and I have frequently mentioned it to my students. It has always been a matter of interest to me that an event so definite, one which must be familiar to many clinicians and physiologists, has not been more generally recognized.

Barié,[2] indeed, in 1893, says: "If one auscult a large number of healthy individuals, one perceives that the long pause is not absolutely free from sound but that there may be heard a slight rudimentary sound, barely perceptible, which if exaggerated will give rise to gallop rhythm." Within the last year the sound has been noted by several observers. Hirschfelder, in an article on "Some Variations in the Form of the Venous Pulse,"[3] describes two cases in which a wave was observed in the jugular pulse immediately after the fall following the so-called *v* wave — i.e., the fall following the opening of the auriculo-ventricular valves — between this and the *a* wave of auricular contraction. In one of these cases, "... the heart sounds were loud and clear, but at the end of expiration a very faint third sound, coinciding with the time noted in protodiastolic gallop rhythm, was audible in the tricuspid area, at the time when the venous pulse was taken. This sound was not loud enough to be definite,

and none of the tracings which I have made at other times upon cases with gallop rhythm have shown this peculiar variation; so that as yet no definite conclusions as to the relations of this unusual wave of the venous pulse to either the closure of the tricuspid valve or the gallop rhythm are warrantable." Hirschfelder, however, calls attention to the probable correspondence of this wave with the shoulder of the cardioplethysmogram and the time at which the mitral and tricuspid valves are, according to Henderson, closed by the floating together of the cusps.

Recently, an interesting note has appeared by Einthoven,[4] " On a third heart sound." While studying the heart sounds by means of his string galvanometer, Einthoven met with a case in which vibrations were recorded occurring at a period in diastole similar to that in which our sound is audible. These vibrations began on an average 0.13 (.11–.15) second after the beginning of the second sound, and 0.32 second before the beginning of the following first sound, that is, somewhat before the end of the first third of diastole with a pulse rate of 73.

A. J. Gibson,[5] of Oxford, has also observed and well described a similar sound. Gibson's article is interesting, not only because of his excellent description of this sound, but because, although approaching the subject from a somewhat different standpoint, his conclusions as to the probable cause of the phenomenon are similar to ours which were reached quite independently from

him and before the publication of his article; they are also similar to the explanation hinted at by Hirschfelder. Gibson met with the sound in the course of some studies upon a wave of the jugular pulse similar to that described by Hirschfelder. At approximately the same time at which this wave appears, he detected in two cases, "... a third sound between the second sound and the succeeding first sound. It was heard only at the apex in one, while in the other case it was heard at the apex and over the jugular pulsation in the neck. The sound is by no means easy to hear; extraneous sounds must be eliminated as far as possible and special attention paid to the interval in which the sound is expected. Nor is it possible to hear the sound at every systole; from my own observation it is best heard in the short interval between expiration and inspiration. The quality of the sound is low pitched and clear with no suspicion of harshness or anything suggesting a murmur. Except for the pitch it recalls in type the second sound as heard in fat persons. It is slightly increased in intensity and raised in pitch by pressure on the abdomen."

Our interest in this subject was accentuated in November last in the course of some studies which we were making upon the dog's heart. At this time it was accordingly determined to note all cases in which an early diastolic sound and shock were observed in apparently normal hearts. The results of some of these observations which form the basis of this communication were pre-

sented before the Æsculapian Club in Boston in December, 1907, but are now published for the first time.

During four months, in the course of ordinary ward visits and in my consulting room, I have met with 24 cases in which an early diastolic sound was heard in an otherwise apparently normal heart.

The condition of the patients at the time of examination was as follows:

Incipient tuberculosis (afebrile),		1
Convalescents, on the eve of discharge from hospital:		
From slight arthritis,	3	8
,, appendicitis (operation),	1	
,, typhoid fever,	2	
,, catarrhal jaundice,	1	
,, obscure hæmaturia,	1	
These patients were, to all intents, healthy individuals.		
Healthy individuals, — A physician (Hirschfelder's case),		
A healthy hospital employee in whom the third sound had been discovered while convalescent, some weeks before, from influenza,		
A laboratory assistant in whom the sound was discovered after the man had been used as an example of a normal individual in the preparation of the tracings shown in Fig. 2,		
A healthy boy of fourteen brought to my consulting room by an over-anxious parent,		4

Cyclic albuminuria, with normal heart and blood pressure,	2
Exophthalmic goitre, a mild incipient case with an apparently normal heart and pulse rate,	1
Chronic tonsillitis,	1
Neurasthenia,	1
Overwork and debility,	1
Chronic appendicitis,	1
Cholelithiasis, in a period of rest,	1
Rather delicate girl with suspected tuberculosis,	1
Nervous, but otherwise healthy boy of fifteen,	1
Chronic adenitis (Hodgkin's disease?),	1
	24

The *ages* of these patients were as follows:

First decade,	1
Second ,,	11
Third ,,	8
Fourth ,,	2
Fifth ,,	2

The youngest individual was five years of age; the oldest, forty-four.

The *pulse*, of normal rate in all cases, tended rather to be slow than rapid; the rate ranged between 50 and 88 to the minute.

The blood pressure was within normal limits in all cases, tending to be rather low than high.

The averages for each decade were as follows:

	Maximum.	Minimum.
First decade,	100–115	(1 case)
Second decade,	106.6 (9 cases)	78.8 (7 cases)

(In the seven cases in which the minimal pressure was taken the maximal pressure averaged 110.)

Third decade, 114 (8 cases), 77.5 (6 cases)

(In the six cases in which the minimal pressure was taken the average maximal pressure was 119.6.)

Fourth decade, 135 (1 case) 95 (1 case)

Fifth decade, 120 (1 case) 78 (1 case)

In some of these cases the sound was heard only when the patient was lying on his back or on his left side, disappearing in the erect posture. In some it was heard in all postures. In most it was increased in intensity in the left lateral decubitus. In all cases the sound was loudest at the point of maximal impulse in the region of the apex; in several it was heard to a lesser extent over the right ventricle. In none was it audible at the base.

In several cases it was associated with a distinctly palpable shock limited to the point of maximal impulse. This shock was actually visible in a few of these instances. While examining one case in which the third sound was especially clear (the case from which the tracing in Fig. 4 was taken), the stethoscope was handed to a second-year student who had never examined a heart, and was quite unaware of the existing conditions. The student heard the sound and described it accurately.

The early diastolic sound in the dog.— But it is

not only in the human heart that a sound may be heard at this period. I have three times observed similar sounds in the normal dog's heart. To the first case reference has already been made, —a dog studied with Dr. MacCallum two years ago. In this instance cannulæ had been inserted in the left femoral artery, the appendage of the left auricle and into the peripheral part of a severed branch of the pulmonary artery. By so doing the heart was slightly rotated over toward the right, while the left auricle was held rather tensely in position by the cannula in the auricular appendage. There then became audible in the left auricle and just below the valves a first, second, and then, after a momentary pause, a third sound, a diastolic rumble in every way similar to the early diastolic murmur heard in some cases of mitral stenosis. Gradually the murmur disappeared, and one heard only a thud which became clearer with the decreasing rate of heart's action. One was able to observe systole of the ventricle, immediately followed by the second sound which occurred while the ventricle was still in a state of contraction. Then followed the sudden dilatation of the ventricle which occurred abruptly with a distinct shock, having altogether the appearance of an active muscular process. Synchronously with this shock occurred the third sound, the character of which was precisely that of the sound in protodiastolic gallop rhythm heard under so many circumstances. We were able in this case practically to see the association

of this sound with a definite moment in the heart's cycle, that is, the shock of what seemed almost like an active diastole.

Since this time Dr. Stewart and I have had two similar experiences. In the first case, at the outset of some observations upon the heart of a small fox terrier, the sounds were found to be perfectly clear. During the process of opening the chest there was an unusual amount of hæmorrhage. When the heart was exposed, with a pulse rate of about 100, a distinct third sound was audible over the left ventricle; it was not heard over the right chamber. This was exactly like the early diastolic sound in the human being, a slight dull thud following the second sound after a period somewhat less than that which separates the first from the second sound. In this instance the dilatation of the ventricle with diastole appeared to be rather rapid but by no means as strikingly so as in the previous case. An attempt was made to study the effects of vagus stimulation. The response was curiously slow and unusual. Stimulation at first produced no result, but, after removing the electrode from the nerve, the heart stopped. With resumption, the first fifteen or twenty beats were very slow, and during these beats, the third sound was more distinct. On large doses of strychnine the heart was seen to draw itself together visibly. The diastolic relaxation was much diminished; the rate rose to about 120; the sound wholly disappeared. Necropsy showed no abnormalities.

In another dog in which this sound was present, a slight interruption in the dilatation of the ventricles could be seen if one fixed the attention on a bit of epicardial fat on the surface of the right ventricle as it moved under the unopened pericardium. The sound appeared and disappeared at various times during the observation, and the auscultatory changes could always be controlled by the appearance or disappearance of this slight irregularity in diastole. It was evident that the first part of the filling of the ventricle, that before the interruption, was by far the most rapid, and the third sound occurred clearly in association with this rapid filling.

* * *

How may we account for this early diastolic sound and shock heard and felt so often in human beings and observed in these three instances in dogs? Although during the last twenty years I have often heard the sound in apparently healthy individuals, the explanation of the phenomenon has never seemed clear. Two years ago both Dr. MacCallum and I were struck by its association with what appeared to be a very sudden diastole, so sudden that it seemed to us as if it might almost be an active muscular process, and we asked ourselves whether it might not be a muscular sound due either to active diastole or to the tension of a distended ventricle associated with the sudden entrance of blood from the auricle. The conception of an active

muscular diastole we may probably dismiss. There is no direct evidence to support the idea.

In considering the cause of this sound and shock in early diastole it may, however, be interesting to inquire into:

(1.) The exact time relations of the sounds.

(2.) The relation of the third sound and shock to the events observed on the cardiogram.

(3.) Their relations to the jugular pulse.

(4.) Their relations to the volume curve of the distending ventricle.

(5.) Their relations to sounds and shocks heard and felt at this period under various pathological conditions.

(1.) *The time relations of the sound.* — As to the first of these points it will be impossible to speak until we shall have obtained a registration of the heart sounds such as is possible only with an instrument analogous to Einthoven's string galvanometer. Einthoven in his case, in which the pulse varied from 73 to 81 to the minute, found that the average time between the beginning of the first and that of the second sound was 0.33 second. The relation of the length of systole to the length of the whole cardiac cycle was as 0.33 : 0.80 or about as 41 : 100. The beginning of the third sound which, it should be remembered, was in this case inaudible, occurred 0.13 second (0.11–0.15) after the beginning of the second sound, and 0.32 before the beginning of the following first sound. The length of the

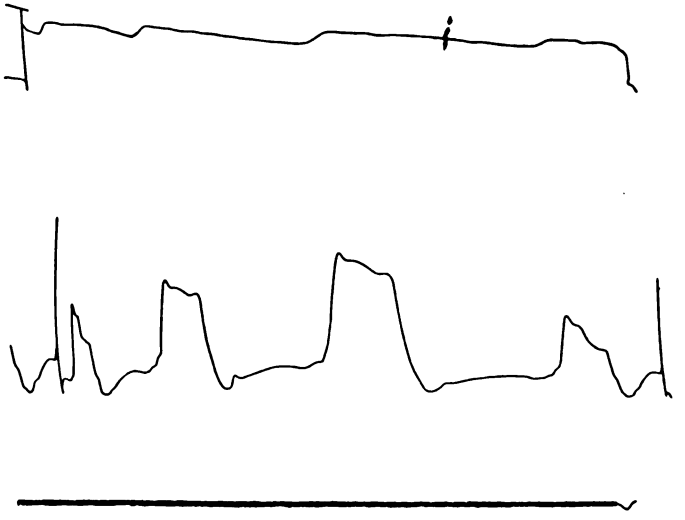

FIG. 1. Normal cardiogram showing protodiastolic and presystolic elevations.

diastolic elevation on the cardiogram, we have sought to determine the time of its occurrence on the curve of the jugular pulse. As a result of the study of seven simultaneous cardiographic and venous tracings taken from six individuals, with apparently normal hearts, in whom an early diastolic sound was audible, it has been possible to determine, within fairly definite limits, the events in the venous pulse which correspond to the protodiastolic elevation.

The normal jugular pulse (Figs. 2, 3, 4) shows three marked elevations. The *a* wave which corresponds to the auricular systole, is closely followed by the *c* wave which marks the onset of ventricular systole. The *c* wave is succeeded, during systole, by a deep depression associated with the emptying of the heart and the pulling down of the auriculo-ventricular valves by the papillary muscles. This depression is followed by an abrupt rise, the so-called *v* wave, near the base of the ascending limb of which occurs the closure to the aortic valves. The summit of the *v* wave at which point occurs the opening of the auriculo-ventricular valves, is followed usually by a sharp fall and then a plateau or a slight gradual rise up to the time of the next *a* wave. Other waves may occur during this period. One which has been pointed out especially by Hirschfelder, and subsequently by Gibson, may occur immediately after the depression following the *v* elevation. This has been called by Hirschfelder the *h* wave.

In these six cases the onset of the protodiastolic elevation on the cardiogram, during which the third sound occurs, is found when allowance is made for transmission time, to correspond invariably to a point somewhere on the katacrotic limb of the *v* wave. Sometimes this is near the summit; usually nearer the base; sometimes

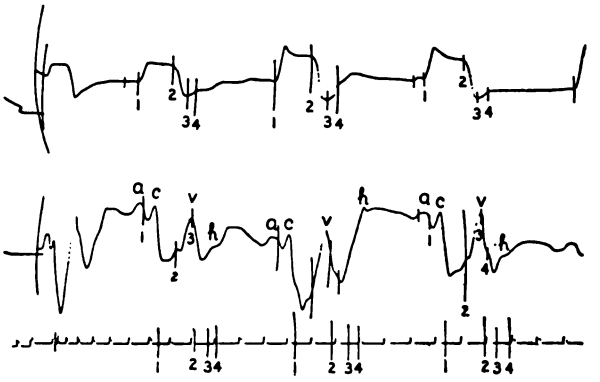

FIG. 2. Cardiogram and jugular curve from a healthy man of nineteen who showed a slight early diastolic sound.
a, *a* wave. *c*, c wave. *h*, *h* wave. 1, beginning of systole. 2, approximate end of systole. 3, beginning of protodiastolic wave of cardiogram. 4, summit of protodiastolic wave of cardiogram.
Transmission time may be estimated by measuring the period between 1 and the beginning of the *c* wave on the jugular curve. Time marked in ½ seconds.

almost at the base. The summit of the protodiastolic elevation corresponds, after allowing for transmission, to the base of the *v* wave or to a point on the plateau or elevation following this. It is interesting that in five of these six cases an *h* wave was present.* Four times it was a well-marked elevation; once it was but slight

and inconstant. In the sixth case in which the third sound was but slight, there were, at one or two points, slight suggestions of an *h* wave. In three of the tracings the summit of the proto-diastolic elevation, with allowance for transmission, reached, with some beats, a point on the anacrotic limb of the *h* wave.

(4.) *The time relations of the sound and shock and protodiastolic elevation on the cardiogram to the cardio-plethysmogram.* — The important observations of Yandel Henderson[7] have demonstrated that diastole is, in most instances, a considerably more rapid process than has generally been assumed. His observations, which have been confirmed in many points by Stewart,[8] in his studies of aortic insufficiency in the dog, show that a large part of the filling of the ventricle may, in some cases, occur in the first moments of diastole in a very short period of time, the plethysmogram showing an abruptly ascending limb indicating a rapid dilatation of the ventricle, followed by a fairly definite shoulder, after which the filling is more or less gradual up to the time of auricular systole when there is again a slight rise in the volume curve. Occa-

* On looking over our tracings a few days before sending our manuscript to the printer, it was found that there was no record of a jugular pulse showing the *a*, *c* and *v* elevations alone, which was suitable for publication. Dr. Eyster and Dr. Stewart accordingly kindly consented to take the tracing which is shown in Fig. 2, from a healthy laboratory assistant of nineteen. On examination of the tracings, a well-marked proto-diastolic elevation was found on the cardiogram, and an *h* wave in the venous pulse. As Dr. Stewart informed me that he had not made a careful examination of the man's heart, I asked him to come to my consulting room at the end of his day's work. He was found to have a most characteristic third sound.

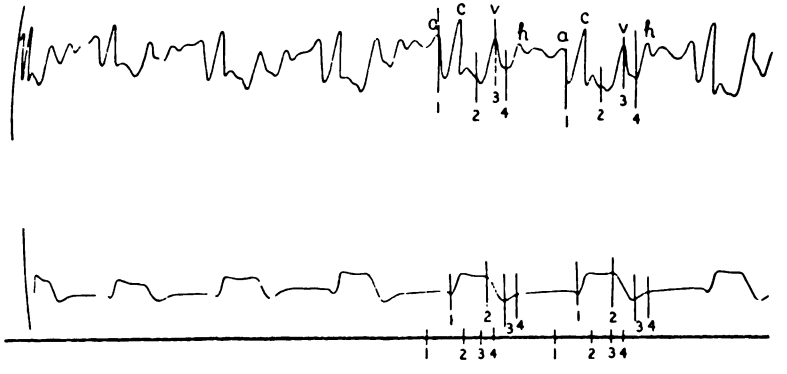

FIG. 3. Cardiogram and jugular tracing from a healthy physician of thirty-five who showed an early diastolic sound (Hirschfelder's original case).

a, *a* wave. *c*, *c* wave. *v*, *v* wave. *h*, *h* wave. 1, beginning of systole. 2, approximate end of systole. 3, beginning early diastolic wave. 4, summit of early diastolic wave.

Transmission time may be estimated by measuring the period between 1 and the beginning of the *c* wave on the jugular pulse.

Time marked in 1-50 seconds.

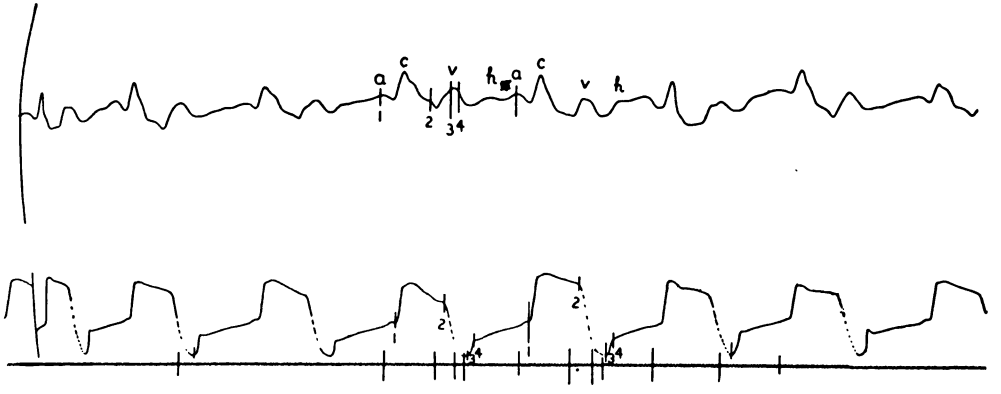

FIG. 4. Cardiogram and jugular tracing from a healthy individual of eighteen with an early diastolic sound of great distinctness.

a, *a* wave. *c*, *c* wave. *v*, *v* wave. *h*, *h* wave. 1, beginning of systole. 2, approximate end of systole. 3, beginning of protodiastolic wave of cardiogram. 4, summit of protodiastolic wave of cardiogram.

Transmission time may be estimated by measuring the period between 1 and the beginning of the *c* wave on the jugular tracing.

Time marked in 1-50 seconds.

sionally, the filling is so complete in the early part of diastole as almost to justify Henderson's somewhat schematic division of the long pause into *diastole* and *diastasis*. In such plethysmograms the ascending limb of the volume curve rises almost vertically to a point nearly as high as that maintained at the end of diastole, and terminates in a sharp shoulder, the summit remaining nearly flat until the slight rise associated with auricular contraction.

The evidence offered by the plethysmogram of a sudden change in the rapidity of dilatation of the ventricle occurring in the early part of diastole, appeared to me interesting in connection with the time of occurrence of the early diastolic sound and shock with which we have been concerned. And, indeed, on studying various plethysmograms made by Dr. Stewart from the hearts in dogs with and without aortic insufficiency, and plotting on these, the time at which the various events of the heart's cycle should fall, it was found that an abrupt shoulder, when present, coincided closely with the period at which the protodiastolic elevation is observed on the cardiogram. The period of time elapsing between the foot of the ascending limb of the plethysmogram, at which time aortic closure should occur, and the shoulder amounted, in one instance, to a period as short as 0.15 in a pulse of 85. This may be compared with our Case VII, in which, in a little girl five years of age, with a pulse of 87, the summit of the proto-

diastolic elevation fell 0.15 second after the shoulder of the cardiogram.

In an attempt to throw further light on this question the plethysmogram of a normal dog's heart was taken by Henderson's method, while synchronous records were made of the carotid pressure and of the pressure in the right auricle by means of a Fredericq sound introduced through the jugular vein. Unfortunately, the heart's action was very rapid and diastole so shortened that it was impossible to study the relations properly. With vagus stimulation, however, some observations were made which, while they must perhaps be accepted with reserve, are yet not devoid of interest. In such curves, where the early part of diastole is rapid and the shoulder on the cardiogram is well defined, the *c* wave in the venous pulse corresponds exactly with the beginning of the systolic fall. The dicrotic notch on the carotid tracing occurs, with allowance for transmission time, just at the foot of the ascending limb of the plethysmogram. The *v* wave of the venous pulse begins just before the end of systole, while its summit falls at a point a little way up the ascending limb. The shoulder of the volume curve falls on the katacrotic limb of the *v* wave near the beginning of or on a shoulder analogous, apparently, to the *d* wave of Bard. In other words, the relations of the cardio-plethysmogram to the jugular pulse tend also to show that the shoulder of the volume curve corresponds closely, as to its time of occur-

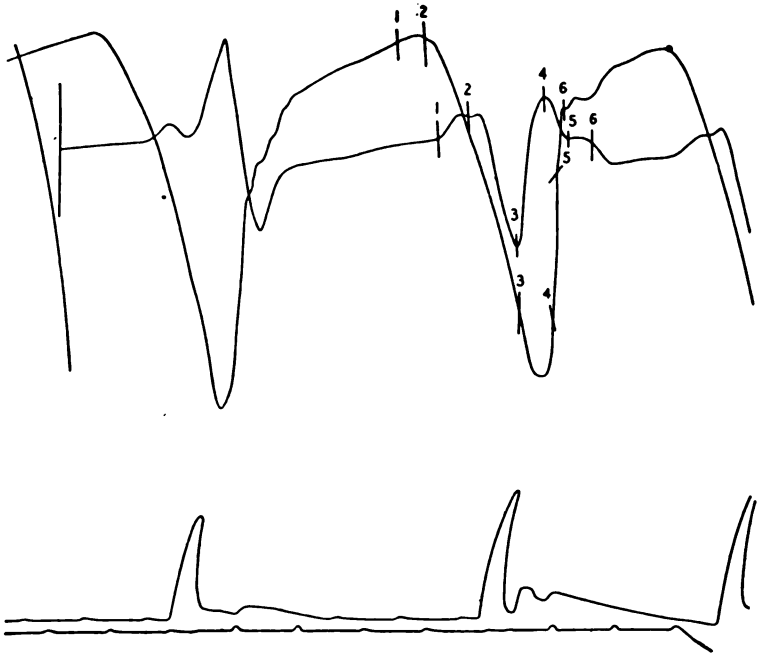

FIG. 5. Cardioplethysmogram, right auricular pressure and carotid pressure of a dog. It will be seen that the shoulder of the plethysmogram (6) falls at a point on the katacrotic limb of the *v* wave (6) approximately in the same position as in a human being. The shoulder on the katacrotic limb of the *v* wave is not dissimilar to the *d* wave of Bard.

The second shoulder immediately following 6 corresponds exactly with the base of this wave.

rence, with the summit of the protodiastolic elevation of the cardiogram.

(5.) *The relations of the normal protodiastolic sound and shock to similar events observed at this period in various pathological conditions.* — When one considers the time at which this additional sound and shock occur, as well as the character of the sound, one is immediately struck by the analogy which exists with sounds heard during the long pause of the cardiac cycle in a variety of pathological conditions.

(*a*) *The so-called opening snap of mitral stenosis.* In mitral stenosis the diastolic murmur begins often shortly after the closure of the aortic valves, with a short, sharp sound associated with a shock closely analogous to that occasionally observed in normal hearts. Although as a rule the sound is sharper than the normal third sound, there are instances in which its character is very similar. Sometimes this " opening snap," as it is called, is distinct in the absence of a murmur. This sound was first noted by Sansom, who says:[9] " It is a sound of tension due to the first inrush of blood into the ventricle, such inrush being more sudden and forcible than under normal conditions, from the increased blood pressure in the left auricle, due to the constriction of the mitral orifice." The sound is well described by Potain:[10] " After the second sound of the heart the diastolic silence begins; during this silence the mitral valve opens; the blood passes from the auricle into the ventricle. Normally there

is nothing to indicate the succession of these phenomena. In mitral stenosis, and especially if the stenosis be of moderate degree, the mitral valve, through the adhesion of the leaflets at their extremities, is arrested in the act of opening, and at this moment is thrown into a sudden tension by the action of the blood rushing through the auriculo-ventricular orifice. This sudden tension determines then the sound, distinct, short, snapping, which follows the second sound of the heart and is of maximum intensity at the apex. These characteristics distinguish it from reduplications of the second sound, the maximum intensity of which is at the base. It is through failure to make this distinction that certain authors have been led to assert that this reduplication is sometimes heard best at the apex. It is evident that in the cases observed by them there was a normal second sound followed by an opening snap. These same characteristics distinguish it also from gallop rhythm. The sound is clear; that of gallop rhythm, dull. . . . From the standpoint of diagnosis the opening snap is a part of the other signs of mitral stenosis, preceding always a more or less marked diastolic rumble."

Although Potain's hypothesis might well explain the origin of the sound in rather highly developed constrictions with great thickening of the valves, it is difficult to see how it could well apply to those cases in which there is but moderate stenosis. The valve here could hardly

be "arrested in the act of opening." In many cases the actual narrowing of the valve is not very great although the shortening of the chordæ tendineæ may be considerable. In the course of diastole in the normal heart it is probable that with the first rush of blood into the ventricle and the rapid dilatation of its walls, the valves, borne up on the entering blood, are brought rather suddenly into a position at least approaching apposition. If then, as is true in most cases of mitral stenosis, there is a greater or less shortening of the chordæ tendineæ, it would seem easily conceivable that with the initial rush of blood from an engorged auricle, the valves might be arrested in their upward course and thrown into a tension sufficient to produce this sound. And this moment would be just that at which the mitral diastolic murmur should begin, associated with the further passage of blood through the then narrowed orifice.

It has seemed to me that in some cases of mitral stenosis the opening snap followed the second sound at a period somewhat earlier than that at which one ordinarily hears the early diastolic sound.

The cardiogram of mitral stenosis with opening snap shows a well marked exaggeration of the protodiastolic elevation. We have not a sufficient number of satisfactory tracings to justify the expression of an opinion as to whether this elevation follows the second sound more closely than in a normal cardiogram. This was

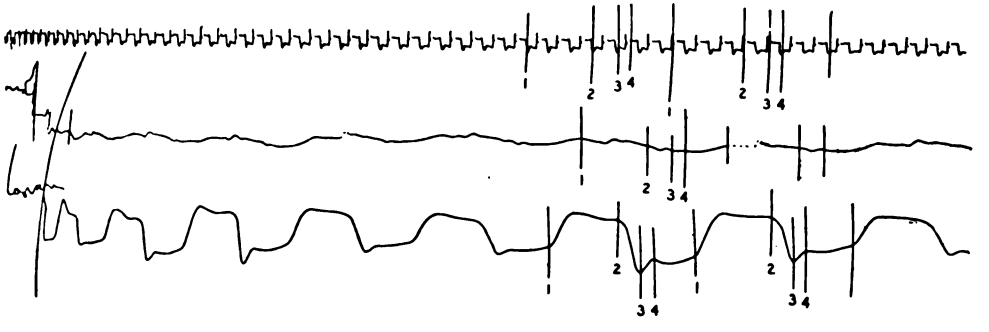

FIG. 6. Cardiogram from a case of mitral stenosis showing a well-marked protodiastolic elevation.
1, beginning of systole. 2, approximate end of systole. 3, beginning of protodiastolic elevation. 4, summit of protodiastolic elevation.
The venous tracing is of no value.
Time marked in 1-10 seconds.

not the case in the patient from whom the cardiogram in Fig. 6 was taken. It would be well worth while to study the relation in time of the protodiastolic elevation to the shoulder of the cardiogram in a series of cases of mitral stenosis.

(*b*) *Protodiastolic gallop rhythm.* — Potain,[11] fifteen or twenty years ago, pointed out clearly that there were two distinct, principally different, forms of gallop rhythm, the one *presystolic* in time, the other *protodiastolic;* the one associated on the cardiogram, with a wave which immediately precedes the systolic elevation, the other associated with a wave which follows closely upon the base of the katacrotic limb. H. Chauveau [12] and F. Müller [13] have called attention to the fact that "these two points in the diastolic part of the cardiogram in which higher waves are seen in gallop rhythm, are also usually marked on the apex curve of the normal heart by evident but smaller elevations; and one must assume that the larger waves which distinguish the cardiogram of gallop rhythm represent a pathological exaggeration of movements which are also appreciable in the normal heart."[14] Protodiastolic gallop rhythm is observed in some dilated hearts, especially in aortic insufficiency, as well as in certain cases in which there is reason to believe that there are myocardial changes, notably in the course of or just after acute infections, as in typhoid fever.† The third sound occurs shortly

† Further studies as to the relations between presystolic and protodiastolic gallop rhythm, and especially concerning the clinical conditions under which each form occurs, are highly to be desired.

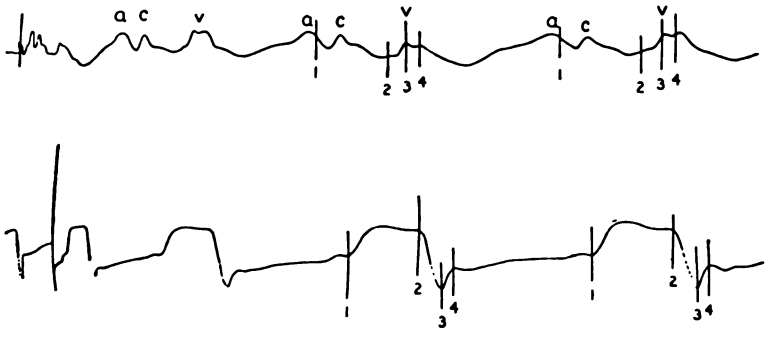

FIG. 7. Cardiogram and jugular tracing from a man about twenty-five, with acute polyarthritis showing a protodiastolic gallop rhythm and shock.

a, *a* wave. *c*, *c* wave. *v*, *v* wave. 1, beginning of systole. 2, approximate end of systole. 3, beginning of early diastolic wave. 4, summit of early diastolic wave.

Transmission time may be estimated by measuring the period between it and the beginning of the *c* wave of a jugular pulse. The *v* wave of this tracing has a peculiar bifid summit. There is no distinct *h* wave.

after the second at the same period in which the early diastolic sound is sometimes observed in normal hearts. (Fig. 7.)

In *aortic insufficiency* the sound is often associated with a well-marked shock at the apex, a shock which may frequently be accurately timed by placing one hand at the apex of the heart and another over the pulmonic valves. It then becomes possible to make out the 1, 2, 3 rhythm which is audible at the apex: (1) the long, slow, systolic impulse, the so-called *choc en dome*, associated with the dull, humming first sound of aortic insufficiency; (2) the closure of the basic valves, easily felt by the hand in the pulmonic area, which is synchronous with the feeble second sound heard at the apex, and in this area often unaccompanied by the early diastolic murmur audible over the right ventricle, at the base and in the axilla; (3) the sudden relaxation of the ventricle followed rapidly by a definite shock which is coincident with the third sound. In some cases this sound is distinct and well defined; in other instances, dull and thudding. Just about the apex it is often followed, in aortic insufficiency, by the humming, echoing Flint murmur. In the axilla where the Flint murmur, even if present over the ventricle, is often absent, the third sound frequently becomes clear, giving rise to a distinct protodiastolic gallop rhythm. In aortic insufficiency then, the sound varies from a loud echoing rumble to a fairly well defined, short sound or a slight distant hum more appre-

ciable to the ear as a shock than as an actual sound. In other words, it is sometimes exactly similar to the third sound heard in normal hearts. Cardiograms from cases of aortic insufficiency with early diastolic sound and shock show a well marked protodiastolic elevation. In the tracings from L. B. (Fig. 8) it was found that the onset of the elevation occurred 0.15 and the summit 0.22 second after the shoulder of the cardiogram. On the venous tracing the protodiastolic elevation corresponds to a part of the katacrotic limb of the *v* wave, the summit occurring usually toward the base of the anacrotic limb of an *h* wave, just as was observed in the normal cases.

(*c*) In *adherent pericardium* a third sound is frequently associated with a well-marked shock occurring in early diastole. This shock, often ascribed to a thoracic rebound, has been shown by Brauer[15] to occur as well when thoracoplasty has been performed. As shown in Brauer's tracings, the elevation on the cardiogram corresponding to the protodiastolic shock may be the most striking feature of the record. In Figs. 9 and 10 may be seen the cardiogram, carotid and jugular tracings from a case of adherent pericardium with protodiastolic gallop rhythm. The period between the second and third sounds in this case was notably short.

The systolic retraction, easily detected by the eye and finger, is evident in the tracings. The enormous protodiastolic elevation begins shortly after the closure of the aortic valve and, when

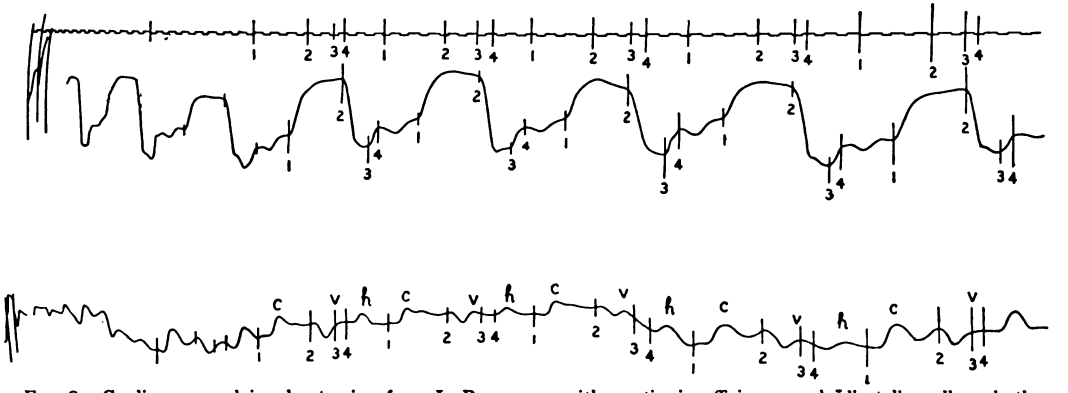

FIG. 8. Cardiogram and jugular tracing from L. B., a man with aortic insufficiency, early diastolic gallop rhythm and Flint murmur.

c, *c* wave. *v*, *v* wave. *h*, *h* wave. 1, the beginning of systole. 2, approximate end of systole. 3, beginning of protodiastolic elevation. 4, summit of protodiastolic elevation.

Transmission time may be approximately estimated by measuring the period between it and the beginning of the *c* wave on the jugular curve.

There is evidently a considerable carotid element in the venous curve.

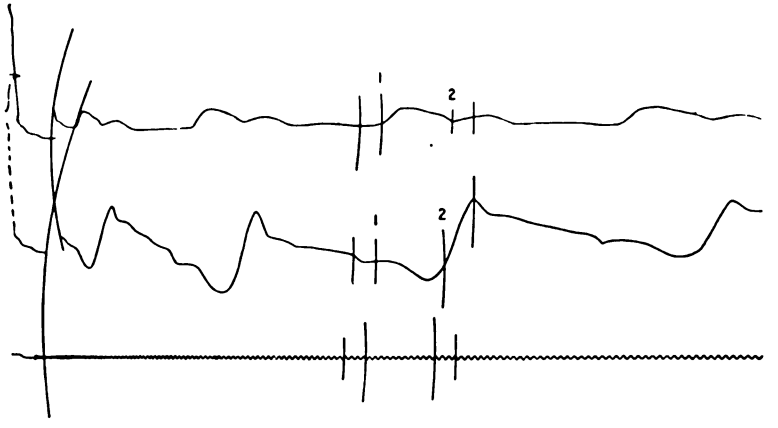

FIG. 9. Cardiogram and carotid tracing from M., a man of about forty, with adherent pericardium, early diastolic sound and shock.

The onset of systole, if *Anspannungszeit* and transmission time be allowed for, may be seen to precede immediately a depression on the cardiogram. Aortic closure with allowance for transmission time comes at the bottom of, or just before, the bottom of the systolic depression. This is followed by an exceedingly abrupt elevation, the summit of which is reached .16 to .17 second after the aortic closure. The marking on the tracing which was made to represent the beginning of systole, i. e., that preceding the line marked 1, is at least 0.02 too near 1. As much as .10 should be allowed for *Anspannungszeit* and transmission.

Time marked in 1-50 seconds.

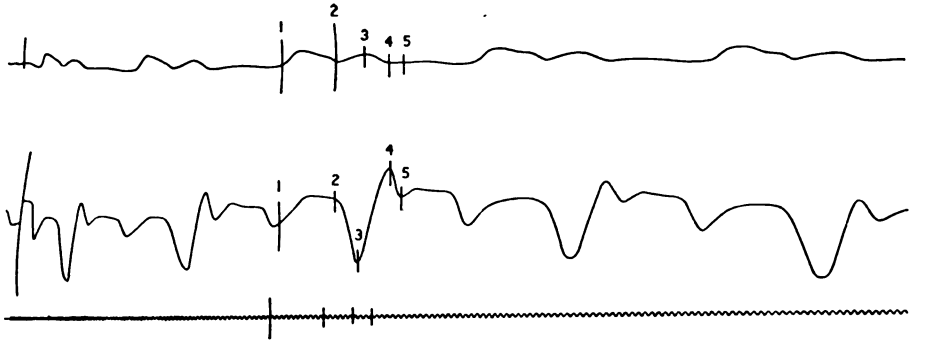

FIG. 10. Carotid and venous tracing from M., a man of about forty with adherent pericardium, early diastolic sound and shock. The aortic closure, when allowance is made for transmission time, is followed soon by a very sharp depression. The base of this depression corresponds in time to the summit of the protodiastolic elevation on the cardiogram. This point falls on the jugular curve just at the base of a very abrupt and high wave, the summit of which is marked by the figure 4.

allowance is made for transmission, is represented on the venous tracing by a marked fall. The summit of the protodiastolic elevation, which occurs 0.165 second after the dicrotic notch, corresponds to the foot of the anacrotic limb of an abrupt and lofty elevation of the venous pulse.

*

* *

If now we consider that which has gone before, the following assertions appear to be justified:

(1.) In healthy young individuals a third heart sound is often audible in the early part of diastole.

(2.) This sound is not infrequently associated with a shock which may be not only palpable but visible.

(3.) The sound and shock are evidently closely connected with the protodiastolic elevation of the cardiogram which was well marked in all of our tracings.

(4.) The onset of this elevation occurred, in our tracings, at a period about 0.1, the summit, about 0.18 second after the shoulder of the cardiogram, or 0.42 and 0.5 respectively from the onset of systole in a cardiac cycle, the average duration of which was .914, i.e., a pulse of 65+.

(5.) The protodiastolic elevation on the cardiogram, when allowance is made for transmission time, corresponds in time to a part of the katacrotic limb of the *v* wave of the jugular pulse, its summit reaching, often, a point somewhat beyond this.

(6.) In five out of six of our cases the *v* wave was followed by an elevation corresponding to the *h* wave of Hirschfelder (the *b* elevation of Gibson), and on some of our tracings the summit of the protodiastolic wave would seem to extend to a point on the early part of the anacrotic wave of this elevation.

(7.) The summit of the protodiastolic wave of the cardiogram appears to correspond closely in time, and in its relations to the venous pulse, with the shoulder on the ascending limb of the cardioplethysmogram, which may be well defined in some volume curves of the dog's heart.

(8.) The phenomena associated with the early diastolic sound and shock in normal individuals are, apparently, closely analogous to, if not identical with, those observed in some forms of protodiastolic gallop rhythm. The sound and shock are similar in character and in time, and are associated with like appearances on the cardiogram and in the venous pulse.

(9.) The "opening snap" in mitral stenosis, although usually a somewhat sharper sound, may be very similar in character to the normal third sound; it occurs at much the same period in the cardiac cycle — possibly a trifle earlier — and is associated with a well-marked protodiastolic elevation on the cardiogram.

(10.) This third sound and shock are not dissimilar to those observed in adherent pericardium, which are also associated with a sharp protodiastolic elevation on the cardiogram. In

a striking example of this condition the protodiastolic elevation corresponded, on the venous tracing, to a sharp depression, the base of which, the point corresponding to the summit of the protodiastolic wave, was followed by an abrupt rise on the curve.

In view of these considerations it is clear that the early diastolic sound sometimes heard in normal hearts is an event closely associated with the rapid entrance of blood into the ventricles at the onset of diastole. How rapid this entrance may be is shown by the abrupt ascending limb of some cardioplethysmographic curves.

Now the association of this sound with (*a*) the shock at times felt by the palpating hand; (*b*) the sharp shoulder which may be seen on the plethysmogram; (*c*) the presence in so many of these cases of an *h* wave in the jugular pulse following, as it does, immediately on the summit of the protodiastolic wave of the cardiogram; (*d*) the observations of the dog's heart in which a visible interruption of the dilatation of the ventricle was demonstrable, would all suggest:

(1.) That at just this period, early in diastole, some structure is thrown into sufficient tension to produce audible vibrations.

(2.) That there is, further, at this period some sudden slight, temporary arrest or interruption or delay of the rapid dilatation of the ventricle.

That the sound is due to vibrations of the chest wall is ruled out by its presence in the

exposed dog's heart, as well as by its presence in the heart after thoracoplasty.

It is, moreover, fairly evident that the sound is usually produced in the left side of the heart. It is, as a rule, audible and palpable only at or in the immediate neighborhood of the apex, while in our three cases in dogs it was heard only over the left ventricle — and once in the left auricle as well. That a similar sound may arise in the right ventricle must, however, be admitted.

What structures in the left ventricle might be thrown into vibration at this period? Einthoven's suggestion that the third sound is due to late vibrations of the aortic valves corresponding to waves on the katacrotic limb of the sphygmogram can hardly be accepted. The character of the sound; the position in which it is heard; the well-marked shock which may accompany it; its various analogies with sounds which are unquestionably of other origin,— are sufficient, it would appear, to invalidate this explanation.

Several possibilities suggest themselves:

(1.) One might fancy that with the sudden entrance of a large quantity of blood from the left auricle into the dilating ventricle, there is produced an appreciable impulse, sufficient to cause the protodiastolic wave of the cardiogram; that, at the same time, the walls responding to their sudden distention may offer a slight momentary elastic resistance, being thrown at this instant into vibrations of intensity sufficient to produce the early diastolic sound. The

slight resistance offered at this moment might account for the centrifugal *h* wave of the venous pulse, a wave which ought to be more marked in the pulmonary veins than in the jugular.

This is in some respects an engaging hypothesis. It is true that, in this moment in diastole, there is a rise in intraventricular pressure, but it is exceedingly slight. There are also several objections which may be raised against this idea. In the first place, the character of the sound is often too sharp and definite to be of muscular origin. Again, in mitral stenosis, where, owing to the nature of the lesion, the first rush of blood into the ventricle cannot be as great as under normal circumstances, a closely similar sound and shock are met with.‡ Moreover, the occurrence of the sound in the hearts of patients suffering with or convalescent from febrile diseases, as well as in one of our experiences with a dog's heart, where it appeared with apparent dilatation, increased under vagus stimulation, and disappeared on the administration of strychnine, suggest that the appearance of the sound may be favored by conditions associated with a diminished tonicity of the heart muscle. But this would be in contradiction to the hypothesis of a muscular sound. For in such conditions, the resistance to the first influx of blood should be diminished.

Potain [16] explains the analogous protodiastolic

‡ In instances of slight mitral stenosis the heightened auricular pressure might more than compensate for the narrowing of the orifice, but the presence of the sound in stenosis of a fairly well marked degree could hardly be accounted for by sudden tension of the ventricular walls.

gallop rhythm by the assumption of a suddenly arrested diastole dependent, however, on changes in the heart muscle. To quote his words:

"In the different varieties of gallop rhythm in diastole the abnormal sound always results from the penetration of the blood into the cavity of the ventricle. In the normal condition this penetration is unaccompanied by any appreciable sound even in conditions of great circulatory excitement. For a mass of fluid in movement does not produce a shock except when it is arrested by a sudden obstacle. But the obstacle which arrests the column of blood penetrating the ventricular cavities is the resistance of the wall, and this resistance is represented in the normal heart by the muscular tonicity which gives way progressively. On the contrary, the arrest of the column of blood falling into the cavity of the ventricle is brusque, sudden, and capable of producing a perceptible shock for the hand and for the ear whenever, the tonic resistance of the myocardium being diminished, that of the fibro-connective elements in the wall is thrown suddenly into action at the moment when filling is accomplished. The state of the heart fills the conditions required to give rise to gallop rhythm when its wall is modified in such a manner that the resistance of these latter elements is in excess, either because they have proliferated more or less considerably, as takes place in patients with Bright's disease whose hearts are sclerotic, or because the myocardium

has rapidly degenerated, as occurs, for example, in typhoid fever. And this explains why the same phenomena may be the consequence of two conditions of the heart as different as the rigidity of the nephritic heart and the extreme flaccidity of the heart in certain cases of typhoid fever. Moreover, the fibro-connective resistance of the wall is brought more certainly into play the nearer the heart, constantly dilated, approaches the degree of distention at which its resistance comes into play. This is the reason that in certain patients the gallop rhythm appears as soon as they take the horizontal position and the increased intra-cardiac pressure brings about a notable degree of dilatation. . . . It will depend, therefore, upon the constant pressure, that is to say, the more or less considerable accumulation of blood in that part of the venous system which is near the heart, and also upon the more or less complete evacuation of the ventricular cavities that the diastolic tension of the walls occurs almost at the beginning of diastole or only when auricular systole comes into play, and that the gallop is therefore protodiastolic or presystolic."

This hypothesis is interesting but difficult to prove, and scarcely applicable to normal cases. Moreover, it is difficult to imagine that the limits of distention are actually reached so soon. Although the shoulder of the cardioplethysmogram, the moment at which the arrest in the rapidity of diastole occurs, may be very sharp, I

have never seen an instance in which *no* further dilatation occurred.

Again, the remarkably small limits of variation in the time at which the normal third sound occurs would tend to suggest that, as Müller and Chauveau hold, it depends on the exaggeration of a normal phenomenon rather than upon causes such as those suggested by Potain.

(2.) Another possibility which presents itself, that which appears to offer the most reasonable explanation, is that with the first inrush of blood, the mitral and tricuspid valves, especially the former, borne up on the entering current toward a position of closure, while the ventricular walls are rapidly dilating, may be brought suddenly into a condition of tension sufficient to cause the sound and shock and to give rise to the centrifugal *h* wave.§

If this hypothesis be correct, one might expect to find the sound more frequent pathologically in cases where, owing to a diminished muscular tonicity, the diastole is more sudden, or where, owing to a weak heart muscle, insufficient emptying of the ventricle and high auricular pressure, such an hypothetical early tension of the mitral valves might be especially favored. But these are, indeed, conditions under which protodiastolic gallop rhythm is common.

Such an hypothesis might well explain its appearance in adherent pericardium where dila-

§ This hypothesis, which, as will be pointed out later on, is essentially that of Gibson, was advanced quite independently of his work and before the appearance of his article.

tation is so common and diastole notably rapid, because of the traction exercised upon the ventricles by the adhesions.

This explanation also applies peculiarly well to the similar phenomena occurring in aortic insufficiency. Here there is usually a dilated ventricle, often an engorged auricle, as well as the added element of regurgitation from the aorta, conditions peculiarly fitted to produce an early tension and closure of the mitral valves. And here, indeed, the sound is often followed by the slight vibratory murmur (Flint murmur) so analogous to that of mitral stenosis, in all probability due to fluid veins arising in the blood as it passes through the mitral orifice.

It is by exactly the same hypothesis that we have sought to explain the similar sound in mitral stenosis.

If our hypothesis as to the valvular origin of the early diastolic sound be true, one might indeed ask why in cases of dilatation with engorgement of the auricle the valves might not be brought, early in diastole, into a position so analogous to that which they occupy in aortic insufficiency, as to give rise, with the further passage of blood from auricle to ventricle, to fluid veins sufficient to cause a slightly audible diastolic murmur. But this was indeed true in one of our dogs where, at first, the sound was followed by a distinct murmur. Again, as has already been said, the sound in a healthy human being is sometimes a slight hum, somewhat

longer than the ordinary phenomenon; and indications of such a hum following the sound may sometimes be brought out if the patient turn upon the left side. In adherent pericardium with dilated heart, slight mitral diastolic murmurs without valvular disease have also been described.

Furthermore, I have in one instance met with a third sound, a diastolic murmur in the tricuspid region, which could only be explained by such an hypothesis. The patient was a colored man with arteriosclerosis and dilated heart, but without valvular disease. There was mitral and tricuspid insufficiency due to dilatation of the ventricles. To quote one of my own notes, made in 1905: " In the fifth space, in about the parasternal line, there is heard a distinct mid-diastolic murmur. This begins shortly after the second sound with a slight shock exactly like the opening snap of mitral stenosis, and runs at times almost into the first sound. At other times it stops just before it. It is slightly rumbling and presents all the characteristics of the murmur of mitral stenosis with Flint murmur. It is limited to an area about the size of the bell of a stethoscope. The murmur seems to be more marked during inspiration. No aortic diastolic murmur is to be heard." This murmur, always rather soft, never very intense, was heard throughout the last two years of the patient's life. It was limited to a small area over the right ventricle; never audible at the apex. Its nature was the subject of much discussion, and the only satisfy-

ing explanation which was reached was that with diastole, owing to the dilatation of the ventricle, the tricuspid valves were brought, with the entrance of the first rush of blood, into a condition of tension causing the sound, and thereafter, owing to the production of a slight *de facto* stenosis, the murmur. At the necropsy, both right and left ventricles were dilated and hypertrophied; there were no valvular lesions. This is the only instance in which I have observed such a shock and sound limited to the right ventricle.

That the phenomenon is due usually to events taking place in the left side of the heart would well explain the fact that the *h* wave of the jugular pulse is so slight in some cases.

This hypothesis is similar to that hinted at by Hirschfelder[17] as an explanation of his *h* wave.‖ Henderson[18] also assumes that the shoulder of the volume curve is associated with the approximation of the mitral valves. Furthermore, the hypothesis is almost exactly that upon which Gibson relies to explain the sound heard in association with his *b* wave. To quote his words:[19] " By observation on the excised heart it can be seen that as the ventricular cavity fills, the auriculo-ventricular valves float up and close automatically when the ventricle is full, and it is easy to imagine that the inrush of blood would be followed by a reaction on the ventricular walls in proportion to the momentum of

‖ Hirschfelder's suggestion, it should be said, relates to the tricuspid, *not* the mitral valve. The principle is, however, the same.

the inrush, so that with a rapid and full stream the tightening of the valves would be quick and strong while with a slow stream the process would be more gradual yet in no wise less complete. The fact that this explanation necessitates the closure of the valves *before* the auricular beat is no objection; the amount of force necessary to push open the valves is extremely small, and the heart would be the more rather than the less efficient pump because of the double closure of the valves. The sequence of events in the diastolic period would then be as follows: After the replacement of the heart which follows systole and causes the *v* wave in the jugular pulse, the blood flows into the ventricle, the valves float up, gradually when the venous pressure is low, quickly when it is high, and the orifice closes; the auricle is now filled by blood from the veins; it contracts and forces the greater part of its contents into the moderately distended ventricle which then becomes fully so, the valves close again from the increase of pressure set up in the ventricle by the auricular contraction; finally, the ventricular contraction keeps the valves closed till the end of systole."

If this hypothesis be correct, why should the sound be heard in some individuals and not in others, and why should it be especially common in young people? The intensity of the sound is often so slight — so near the borderland of the audible — that it is not remarkable that it is frequently missed. Its apparent frequency in

individuals with a slow, full pulse would appear to be in accordance with the last mentioned hypothesis, and the observation that the sound is sometimes louder during the slow beats of expiration may well be accounted for by the assumption of a higher auricular pressure during this period.

In connection with the increased intensity of the sound in the left lateral decubitus, it should be noted that, in this position, a well-marked systolic apical murmur may be brought out in cases where, in other attitudes, the heart sounds are clear. If this murmur be regarded as indicative of a functional insufficiency of the mitral valve, the third sound may then well be dependent on the more sudden distention of the ventricle with an increased quantity of blood under higher pressure.

There would, however, seem to be no reason to suppose the existence of especially high auricular pressure or of diminished cardiac tonicity in the many healthy young people in whom the sound is heard. I have always fancied that one, if not the main, reason that the sound was so well heard in the young was because of the thinner chest walls, the less voluminous lúngs, and the greater ease with which the heart can be approached.

(3.) There is another possibility with regard to the cause of this sound which may be simply mentioned. Stewart has shown that there is in the normal heart an early diastolic contraction

of the ring of muscle just below the aortic and pulmonic valves, a contraction which serves evidently to reinforce the closure of the arterial orifices. His work has not yet been published, and while one might *a priori* expect that the sound associated with such a contraction, if such a sound indeed there be, would occur at a somewhat earlier period, and that it would be more appreciable at the base of the heart than at the apex, yet in the absence of positive proof of that which we have advanced as the most engaging hypothesis, it may be well to bear in mind the possibility that the contraction of the aortic ring may be a factor in the production of the sound, however improbable it may seem.

SUMMARY.

In many healthy individuals, especially in the young, there is audible at the apex of the heart a slight third sound, which occurs in early diastole shortly after the second sound.

This sound is commoner with a slow pulse; it is better heard in the recumbent posture and, especially, in the left lateral decubitus. It is sometimes more clearly audible during expiration.

The sound is not infrequently associated with a shock which may be visible as well as palpable. The sound and shock occur synchronously with the protodiastolic elevation of the cardiogram which is usually prominent in these cases.

These events cover a period of time represented on the jugular pulse by the later part of the kata-

crotic limb of the *v* wave and, generally, a part of the anacrotic limb of an *h* (Hirschfelder) wave (*b* wave of Gibson), which is usually present in these cases. This period corresponds closely to that occupied by the shoulder of the ascending limb of the cardioplethysmogram.

Conclusive evidence as to the cause of this phenomenon is, as yet, wanting.

From a consideration of the conditions observed in normal individuals, together with various apparently analogous manifestations occurring in disease, we are disposed to incline toward the hypothesis that the sound is produced by a sudden tension of the mitral and, perhaps at times, tricuspid valves occurring at the end of the first and most rapid phase of diastole.

In conclusion I wish particularly to thank my friend, Dr. Eyster, of the Physiological Department, for valuable assistance.

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THE VALUE OF LUMBAR PUNCTURE IN SYPHILITIC AND PARASYPHILITIC DISEASES OF THE NERVOUS SYSTEM.

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IT is now seven years since Monod,[1] working in Brissaud's clinic, and Widal, Sicard and Ravaut [2] called attention to the fact that an increase of lymphocytes in the cerebrospinal fluid of individuals suffering from general paresis and tabes is almost constantly to be found. Following the work of these pioneers a large number of papers have been published, mostly by French and German investigators, corroborative of their work. Besides the increase in lymphocytes, it has been repeatedly demonstrated that serum albumin, which exists not at all or in only slight traces in normal cerebrospinal fluid, is increased in tabes and paresis to from 2 to 4 gm. per thousand.

It is not from lack of appreciation of the constancy of this albumin increase that the writer has omitted this test in many of his cases, but because its performance requires a larger amount of fluid than does the cell count. The fact that all the cases reported in this paper were tested either in the office or in the out-patient clinic rendered it inadvisable to withdraw more fluid than was

necessary in order to obviate the development of uncomfortable symptoms which sometimes follow the operation. Moreover, the proteid estimation, while in itself of value, gives little additional information if the cell count is to be made. It is true that a few cases have been reported where the albumin test was positive and the cell count negative, but in these cases the cell count was made by the old method which lacks the accuracy of our present method of estimation.

As a matter of fact, we know that the number of cases of paresis in which the cell count has failed to show a lymphocytosis is very small. Pomeroy [3] has collected statistics of 500 cases suffering from this disease in which lumbar puncture was performed, and only 2.6% gave a negative result. Cornell, who used the more accurate slide counting method, has had no negative counts in 37 punctures, while Fuchs and Rosenthal [4] had 12 and Rhems [5] had 39 without a negative result. Based on these data, Cornell [6] gives it as his opinion that every case of paresis shows a cellular increase in the cerebrospinal fluid.

Regarding the constancy of the sign in tabes, Fuchs and Rosenthal collected 154 cases in which the sign was positive and 13 in which it was negative, while in their own tabetic case it was positive. Purves Stewart [7] found 8 cases positive and reported 1 case of his own of undoubted tabes in which the count was negative and referred to a negative case of Ferrier and Babinski.

In the light of all that has been done, therefore,

we must accept the fact that a leucocytosis of the cerebrospinal fluid is practically always present in tabes and general paresis, and Joffroy,[8] as well as Marie and Duflos,[9] maintain that it is present in the earliest stages.

The value of this aid to diagnosis has been made use of by some in cases of tabes, but to a much greater extent by psychiatrists in differentiating general paresis from psychoses which may simulate this disease, notably alcoholic psychoses, arteriosclerotic psychoses, dementia precox and psychoneuroses.

The object of this communication is to show by brief abstracts of a few records the sort of cases in which lumbar puncture is useful to the practitioner; to add my endorsement to that of the advocates of the slide counting method; and to call attention to the fact that the test can be made in the office or in the bustle of an out-patient clinic and the results obtained in a few minutes.

I am aware that Pomeroy and Nissl[10] make as their first rule: "Patients should not be punctured unless they can be put to bed." It is here, however, that the advantage of making the count without the corroborative evidence of the albumin test is manifest, for if done by the slide counting method, only a few drops of the fluid are needed, and the occasional results of headache, nausea and malaise may be avoided.

The method of procedure of nearly all the investigators who have employed cytodiagnosis of the cerebrospinal fluid has been to collect the

fluid in a conical-shaped tube and centrifugalize it at a high rate of speed for twenty to thirty minutes. The fluid is then poured off and the tube inverted and allowed to drain until only a small drop remains in the small tipped end. This drop is absorbed by means of a fine capillary pipette and is spread on three coverslips, dried, fixed and stained. The count is then made with a 1-12-in. oil immersion lens and the average number found in a field is estimated.

The results obtained by this method must vary with the time and rapidity of centrifugalization and the technique of the investigator, for it is obvious that the varying size of the drop left in the tube and the character of the spread must give rise to widely different results.

We owe to Fuchs and Rosenthal the introduction of a modification of the Thoma Zeiss blood-counting apparatus, as a more accurate means of estimating the number of cells. They employed the white blood corpuscle counter, drawing a staining mixture up to 0.5 and filling the tube to 11 with the cerebrospinal fluid. For the purpose of staining they used methylene violet 0.1, acetic acid 2, and water 50, which mixture serves to bring out the character of the cells and distinguishes the red corpuscles which may contaminate the fluid. When the fluid has been thoroughly mixed and stained, the count is made on a slide which differs from the ordinary blood counting slide in that the chamber is larger, measuring 4 mm. square and 2 mm. deep. By counting two or three spreads

on such a slide the average is taken and the number of cells per cubic millimeter easily computed.

It has not seemed to me necessary to use the modification of Fuchs and Rosenthal, for in making the count on the ordinary blood-counting slide I have found that if the fluid be well mixed in the pipette that there is very little variation in the count of four or five successive preparations. If the validity of the count is corroborated in this manner the number of cells per cubic millimeter is easily estimated.

The value of this method of counting lies chiefly in its accuracy, allowing the results of one investigator to be compared with those of another without question of any variation depending on technic. In this way it may be possible by collecting a large number of cases to make finer distinctions between a number of conditions in which lymphocytosis has been found, and we do not need to deal with such terms as "positive results," "moderate increase," and "marked increase."

All the evidence goes to show that the normal fluid by the old method of counting demonstrated from no cells to two cells in a field, and by the new method from no cells to three cells in a cubic millimeter. There is nearly always a moderate or marked increase in the number of cells in cases of (1) syphilis with active secondary lesions; (2) syphilis of the central nervous system; (3) syphilitic eye disturbances; (4) tabes; (5) general paresis; (6) tubercular meningitis. In addition

to these an increase may be found in (1) multiple sclerosis; (2) mumps; (3) herpes zoster.

There is little difficulty in making the diagnosis from the clinical picture in this latter group of cases, and this is true also of the secondary stage of syphilis and of tubercular meningitis. The real value of the lymphocyte count lies (1) in those cases where there is a well-developed psychosis in which paresis is to be differentiated from other psychoses; (2) in patients who show beginning changes in character and disposition, where the question of a possible early stage of paresis is suggested; (3) patients having isolated symptoms of tabes, such as retention of urine, paresthesiæ, pains, or crises, but who do not show a sufficient number of characteristic symptoms to make the diagnosis of tabes certain; (4) in differentiating cerebral tumors from gummatous growths.

In the light of our present knowledge, however, where the alternative of syphilis of the brain or cord comes up in diagnosticating paresis and tabes, we cannot depend on the lymphocyte count as an aid, for the cell increase is quite as constant in the syphilitic as in the parasyphilitic affections of the nervous system.

It is true that Stewart, in using the cell-counting slide, believes that the average count in syphilis is lower than that in tabes and paresis, giving as his results:

Syphilis,	7	cases,	average	37.6	per cmm.
Tabes,	8	,,	,,	72.3	,,
Paresis,	4	,,	,,	190.4	,,

The average of 190 in paresis, however, is much higher than Cornell reports, for he found that as a result of lumbar puncture 37 times in 25 cases of paresis that the average number of cells was 52, the individual counts varying from 12 to 216. It is apparent from these figures, therefore, that cytodiagnosis can be of no assistance in differentiating tabes or paresis from syphilis in cases where the count is in the vicinity of 40 or 50.

During the past year I have used lumbar puncture as a means of diagnosis in 30 cases; in only 3 was the operation really painful, and in only 1 were there any unpleasant after-effects. This was due to the fact that the fluid was under such pressure that an unusual amount escaped before the needle was withdrawn. The result was that the man was confined to bed for a week on account of headache and malaise. In many instances the patients went considerable distance to their homes after the operation (Lawrence, Lynn, Lowell, etc.) and no discomfort was felt.

It is surprising how little pain is caused by the introduction of the needle in most of the cases. After scrubbing the lumbar region with soap and water and alcohol, local anesthesia was produced by means of the ethyl chloride spray, and several times the patient has remarked that the introduction of the needle was much less uncomfortable than the rubbing of the towel.

The outlines of the following selected records serve to illustrate the type of case in which the leucocyte count of the cerebro-

spinal fluid is of value as an aid to the diagnosis. In all of the cases the number of polymorphonuclear cells has been below 5%, but since these are always present in some degree, I have made use of the word "leucocytosis" rather than "lymphocytosis" to express the cellular increase.

CASE I. Male, thirty-two years of age. Came to Out-Patient Department of the Massachusetts General Hospital on account of retention of urine. Two years previously he had begun to have difficulty in micturition, and this had increased so that he had been obliged to use a catheter for several months previous to his first visit to the hospital. He had contracted gonorrhea four years previously, but denied knowledge of having had syphilis.

The pupils were equal in size, slightly irregular in outline, and reacted well with accommodation, but not to light. The knee jerks and Achilles reflexes were present. There was no ataxia or Romberg's sign, and no history of darting pains or paresthesia.

The Argyll-Robertson pupil in this case suggests tabes as a cause for the bladder symptoms. This diagnosis could not have been made with certainty, however, without the aid of lumbar puncture, which showed 110 leucocytes per cubic millimeters corroborating the diagnosis.

CASE II. A man thirty-four years old gave a history of having contracted syphilis eight years ago. He came to the hospital in February, 1907, on account of Jacksonian attacks, from which he had been suffering for several months. The attacks were ushered in by an aura of a sense of tightness, starting in the toes of the

left foot and extending up the leg. There was then a tonic spasm of the leg followed by unconsciousness and clonic spasm of the left half of the body. There was no headache or vomiting and no optic neuritis. No history of trauma. The pupils were irregular in outline, the right 4½ mm., and the left 2½ mm. in diameter. Both pupils reacted well with accommodation, but the left reacted sluggishly and the right not at all to light. The left knee jerk was more active than the right and there was ankle clonus on the left side. Sensation was normal in all its forms. There was no tremor of the lips or tongue. The speech was not suggestive of paresis, nor was there the characteristic mental indifference and memory defect of this condition.

The question arose as to whether the symptoms were due to cerebral syphilis or tumor of the brain in the region of the precentral convolution. A lymphocyte count of 35 made it possible to rule out the latter condition and accept the former, although the possibility of the convulsions being an early manifestation of paresis was recognized. As a matter of fact, the attacks have now been absent for a year under a thorough iodide treatment, and the patient has showed no further signs of paresis.

CASE III was that of a man forty-two years old, who had contracted gonorrhea at the age of twenty, but gave no history of having had syphilis. In August, 1907, he ran to catch a car, mounted the running board and stood for a moment, when he suddenly had a sensation of having been struck in the left knee, and knew no more till he came to himself in the hospital. During

the next two months he had attacks of Jacksonian convulsions involving the left side, at intervals of one or two weeks. In some of these he retained his consciousness, and others were observed by attendants. The attacks were ushered in by the left leg drawing up, and a few seconds later a clonic spasm of the left arm. In the course of a few weeks there developed weakness of the left arm and leg, so that he found great difficulty in walking and dressing. There was a moderate degree of headache, but no vomiting. The intellect was clear. Pupils equal and reacted promptly. No optic neuritis. No signs of involvement of cranial nerves. Marked paresis of left arm and leg. The left knee jerk was more active than the right, but there was no ankle clonus. The superficial reflexes were absent on the left side.

Here, as in Case II, we have to differentiate between a localized syphilitic process in the brain and a developing neoplasm in the region of the motor cortex. Examination of the cerebrospinal fluid showed but one cell per cubic millimeter which supported the diagnosis of tumor, and operation was advised, but declined by the patient. Iodide of potassium in doses of 200 to 300 gr. a day were given for several weeks in the forlorn hope that some relief might result, but no improvement has manifested itself in the course of three months.

Case IV was a man of fifty-six, seen with Dr. J. J. Putnam in the fall of 1907. For a year past the patient had been unable to attend to his work of auditing accounts because of his feeling of mental incapacity. He had three distinct complaints: (1) in walking he felt as if some one were pulling down on his legs so it was

hard for him to lift them from the ground; (2) in conversation he was apt to think the first half of what he intended to say and begin talking in the middle of a sentence, and while talking he found it a distinct effort to get his tongue around words. His wife also said that he had a recent habit of leaving his sentences unfinished. (3) He was occasionally overcome with dizziness when things seemed to be blurred and move in front of him, and he was in constant fear lest such an attack seize him in the street.

He denied having had syphilis and used alcohol very moderately. Physical examination showed a stout, muscular man, well preserved for his years. He was very talkative and the speech was somewhat slurring. His conversation and manner were both very suggestive of general paresis. He repeated phrases correctly, however, and was quick and accurate in multiplying figures. There were no grandiose ideas. The pupils were regular, equal and reacted well. The fundus was normal. The tongue and lips showed no tremor. The knee jerks were normal. The examination of the cerebrospinal fluid showed one leucocyte per cubic millimeter.

Although there were no somatic signs of general paresis in the patient, and the leucocyte count was normal, his manner seemed so convincingly that of a paretic that a second puncture was performed two weeks later, but the fluid showed only two cells per cubic millimeter. Relying on the cytodiagnosis in this case it is possible to rule out the diagnosis of paresis, and we are forced to accept either a psychoneurosis or an arteriosclerosis as a cause for the condition.

Case V. A man of thirty-three years came to the hospital complaining only of feeling "nervous." This nervousness could not be defined beyond the fact that he felt irritated because he knew that people talked about him and criticised his actions. A short time previously he had given up his position as engineer because his employer found fault with him for incapacity. He felt physically well, but he noticed that his memory had been poorer than usual for several weeks. For two months there had been strabismus. He denied any history of venereal disease.

Physical examination showed the pupils to be regular in outline, equal and moderately responsive to light. There was paralysis of the left external rectus. The tongue was tremulous, but the speech was clear. The knee jerks were normal. Romberg's sign was absent, and there was no ankle clonus or Babinski reflex.

The man's indifferent attitude while his symptoms were being discussed in his presence was characteristic of paresis, and he found difficulty in repeating test phrases correctly. The leucocyte count from the fluid obtained by lumbar puncture showed 110 cells per cubic millimeter.

We have, then, in cases IV and V, patients presenting symptoms suggestive of an early stage of general paresis, but neither showing somatic signs or sufficient mental change to make this diagnosis a certain one. The absence of any increase in cells in Case IV, however, enables us to eliminate the question of paresis, while the high count in Case V serves to corroborate the suspicion of paresis.

CASE VI. A man of fifty had been coming to the out-patient department of the hospital for two years, complaining of numbness of the fingers and toes. This paresthesia increased so that in the fall of 1907 it had extended up to the hips and involved the upper extremities to the wrists. There had been no pains and no bladder disturbance, but his eyesight was failing. The gait was unsteady and the numbness of the hands incapacitated him for work. There was no memory defect and no euphoria. Various diagnoses of tabes, general paresis and diffuse degeneration of the cord had been made in the neurological department. The pupils were regular, equal and reacted normally. Ophthalmoscopic examination showed the disks to be normal, but a considerable degree of arteriosclerosis of the retinal vessels. The knee jerks and Achilles reflexes were absent, and Romberg's sign was present. No Babinski. Hemoglobin = 70%.

The cerebrospinal fluid showed two leucocytes per cubic millimeter, eliminating the diagnosis of tabes and of paresis and corroborating that of diffuse spinal sclerosis.

CASE VII. A man of thirty-nine years. History of a primary specific lesion twenty years ago followed by secondary signs. This was treated well and faithfully for three years. In April, 1907, he got up one morning with a numb, heavy feeling in the right arm and leg, and fell in trying to go downstairs. During the day the paresthesia and weakness passed off, but returned twenty-four hours later and has persisted since.

He felt heavy and sleepy all the time, and was unable to continue his occupation of mail distributer on account of weakness and awkwardness of his right hand.

During the first two weeks of his symptoms there was constant occipital headache, but no vomiting. He

used no alcohol or tobacco. The pupils were equal, regular and reacted promptly to light and with accommodation. The fundus was normal and there was no hemianopsia. There was right hemiparesis and diminished sensibility to touch and prick on the right half of the body. Ataxia of the right hand was present to a moderate degree. Romberg's sign was absent. The knee jerks, wrist and ankle jerks were all exaggerated rather more on the right than on the left side. The urine examination was normal. The speech was strikingly slurring, but the intellect was alert and keen. No memory defect could be discovered. The leucocyte count of the cerebrospinal fluid demonstrated 50 cells per cubic millimeter.

This case is given to illustrate the type in which it is difficult to differentiate between the late manifestations of syphilis of the brain and a developing general paresis. From the picture presented, either condition may have been the cause, and the cell count is quite within the range found in either disease. Iodide and mercury have been persisted in for a year and all traces of the hemiplegia have practically disappeared. In the meantime there has been no further development of symptoms, and the actual diagnosis must remain in doubt.

Other cases varying in the symptoms presented could be added to the series given above, but the group serves to illustrate the sorts of conditions in which cytodiagnosis, as an aid to diagnosis and in determining the prognosis and treatment, is of great value.

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ACUTE YELLOW ATROPHY OF THE LIVER.

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I HAVE had as patients in recent years three cases of acute yellow atrophy of the liver, in all of which the diagnosis was made during life and confirmed at autopsy, and I have had the opportunity to study and report a fourth case with autopsy through the kindness of Dr. Francis H. Williams, visiting physician at the Boston City Hospital. This is a very unusual disease, rarely seen even by physicians of large hospital experience; and on account of its great rarity it seems desirable to report these cases fully with the autopsy findings, a description of the histological changes in the liver and certain chemical analyses which were made. This will be done chiefly from the clinical point of view, with some remarks on the *nature* of the disease in the light of recent investigations.

CASE I J. E. J., age twenty-three, married, was admitted to the Long Island Hospital Jan. 15, 1901, with a diagnosis of syphilis. He gave the following history: His mother had died of pulmonary tuberculosis; the family was otherwise healthy.

Previous illness. — His past history was negative with the exception of measles and pertussis in child-

hood and recent venereal disease. He was employed as clerk in a wholesale liquor store and drank freely of beer, but was seldom intoxicated. Had gonorrhea with epididymitis three years ago with apparent recovery in about two months. Much promiscuous sexual intercourse up to time of marriage three months ago. Then developed a hard chancre and a month later a characterisitc specific roseola with general malaise. He was treated for syphilis, and when the general eruption faded a few unsightly crusted areas on face and elbow persisted.

Physical examination. — At entrance to the hospital showed a well developed, well nourished individual, about 5 ft. tall, weighing 131 lb. Reflexes were normal, heart and lungs normal, the area of liver and spleen normal, no abdominal tenderness. An ulcer the size of a ten-cent piece was found at the base of the penis. Inguinal and cervical glands were somewhat enlarged. Several red macules or papules with pigmented base were scattered over face, body and extremities. A raised crusted area about the size of a walnut was situated on the forehead over the right eye, and other similar lesions, smaller in size, were found on the upper lip, left nostril and left elbow.

Urine, 1,470 ccm., normal color, acid, 1,018 specific gravity. Albumin and sugar absent.

Mecurial treatment was given, pushed to ptyalism and then diminished one half. This was followed by great improvement in the general condition for four weeks. Then loss of weight, appetite and energy were noted and the crusted skin lesions seemed to increase rather than diminish. Mercury and potassium iodide were given together for a month with tonic and hygienic measures, without improving either general or local conditions. The potassium iodide was given in

ascending doses, three times a day, till 85 gr. were reached. The crusts on face and elbow gradually fell off, leaving scars. and the general condition slightly improved. The patient was able to assist in ward work, take long walks, play ball, etc.

Present illness. — On April 4, nearly three months after admission to the hospital, slight jaundice was noticed in skin and conjunctivæ and the patient complained of general malaise and loss of appetite. There were no distinct gastric symptoms and no pain anywhere.

Physical examination was similar to that at entrance with the addition of jaundice. The liver edge was now palpable just below the costal margin, the gall bladder was not palpable or tender. There was slight diffuse abdominal tenderness.

The patient remained in bed most of the time for the next twelve days. He was dull and depressed and slept much of the time and had anorexia and nausea. Eight days after the onset of the jaundice the liver edge was still palpable below the costal margin. The jaundice remained mild and showed a little variation in depth.

On the 13th day the patient became somewhat irrational and mentally confused, refused to have his temperature taken, spat upon his bed and into his medicine. He had forgotten the name of the nurse and of neighboring patients. This was followed by mental excitement, and on the 14th day developed into delirium and at noon he became semi-comatose. The temperature, pulse and respiration were normal.

At 2 P.M. he vomited once, complained bitterly of headache and then relapsed into profound coma. Slight tonic convulsive contractions of the abdominal muscles and of the right side of the face appeared and

continued several times a minute. In the afternoon the jaundice became more intense, vomiting was frequent, of " coffee grounds " material which contained hematin, and in the evening a half ounce of bright blood. There was bleeding from the gums.

Physical examination showed a very peculiar condition of the liver dullness. In the mammary line a tympanitic note was obtained over the normal liver area and the only area of *iver dullness* found was in the mid-axillary line about two inches in diameter, extending from the seventh interspace toward the costal margin; no tenderness was present (coma). The spleen was not palpable and the splenic area on percussion was normal. There was no ascites or edema of extremities. The pupils were dilated and failed to react, knee jerks were present, no clonus.

The blood on the 15th day showed: hemoglobin, 80%; red cells, 6,640,000; white cells, 12,600.

A differential count of the white cells showed: polymorphonuclear neutrophiles, 76%; mononuclear, 19%; transitional, 4%; eosinophiles, 1%.

The *urine* on the 14th day was as follows: 960 ccm.; color dark; specific gravity 1,013. Reaction strongly acid, considerable sediment. Urophain was much increased Indoxyl increased, Chlorides, 5.90 gm. Total phosphates .50 gm. albumin a trace (1-60%). Sugar absent Albumose absent Bile pigments present in large amount. Bile acids absent.

The sediment contained many hyaline, granular epithelial and fatty casts, numerous renal cells, mostly fatty, free and on casts, much free fat, occasional normal and abnormal blood globules, numerous bilirubin crystals and granules. Slight excess of leucocytes, bladder and neck of bladder cells.

No leucin or tyrosin crystals were obtained by simple

evaporation of the urine or by evaporation and precipitation with alcohol.

Careful quantitative analyses were made showing the total nitrogen excretion in the urine and the proportion of nitrogen excreted as urea, ammonia, and uric acid (using the Kjeldahl, Schröder and Salkowski methods respectively). The following results were obtained (14th day, one day before death):

Total nitrogen excreted, 7.47 gm., and of this 62%, or 4.64 gm., was excreted as urea; 22.9%, or 1.61 gm., as ammonia; 1.6%, or 0.11 gm., uric acid; 13.5%, or 1.00 gm., as residue (by difference).

Compare this with the average normal proportions of nitrogen excretion: 86% as urea, 3.5% as ammonia, 2.0% as uric acid, 8.5% as residue.

The patient remained unconscious during the day, vomiting, at rare intervals, occasionally digested blood, and passing urine and feces involuntarily. The convulsive movements continued, but grew weaker, breathing was labored and stertorous, sweat persisted on the face and the jaundice deepened to a dark orange color. The pulse became irregular and intermittent. The patient died on the afternoon of the 15th day. In the last twelve hours of life the temperature gradually rose to 104°, the pulse to 168 and the respiration to 48. The white blood cells were 23,300 per cmm. two hours before death.

The *autopsy* was performed forty-five minutes after death by Dr. George B. Magrath.

Anatomical diagnosis: Icterus; acute yellow atrophy of the liver; fatty degeneration of the kidneys; fatty degeneration of the heart; ecchymosis of the ileum; interstitial orchitis (?); edema of the brain; red bone marrow; multiple cicatrices of the skin.

Body, that of a man about thirty years of age; length 155 cm.; fairly well developed and nourished; rigor mortis absent body warm; slight lividity of dependent parts pupils equal, 3 cm. in diameter; the skin a general deep yellow color the skin of the middle of the forehead shows an old, slightly depressed scar, 2 cm. in diameter the skin of the body and extremities bears numerous irregularly oval, shallow, white scars, the largest about 1 cm. across.

Upon section, subcutaneous fat 1 cm. in thickness, muscles red and firm; vermiform appendix and mesenteric lymph nodes normal.

Thorax, height of diaphragm fourth rib on right side, fifth rib on left.

Pleural cavities, normal.

Pericardial cavity, normal.

Heart, section of the vena cava and pulmonary veins yields dark fluid blood. Weight 270 gm.; myocardium brownish red, microscopically showing interstitial fat; wall of left ventricle 1.3, of right, .3 cm. in thickness; mitral valve 10, aortic valve, 6, pulmonary valve 6.5, tricuspid valve 12 cm. in circumference depth of left ventricle 8.5 cm. Endocardium, valves and cavities normal. Coronary arteries normal.

Lungs, normal.

Abdomen, peritoneal cavity normal.

Spleen, weight 100 gm.; upon section, dark red, markings distinct; pulp not increased; consistence a little diminished.

Stomach, normal.

Intestines small· the ileum shows several small areas of hemorrhage in the mucosa, otherwise intestinal tract negative.

Pancreas, normal.

Liver, weight 730 gm.; symmetrically diminished in

size; length, 19.5, breadth 13 cm., lower border 6 cm. above the costal margin, lay high up under the diaphragm and rather far back; flaccid, flattening out when placed on a table; general color brown red; the free surface in general smooth, presenting here and there areas of varying size, the largest about 2 cm. across, slightly elevated and of a greenish color; upon section, the general cut surface brownish red; devoid of lobular markings, presenting an even, fleshy appearance; distributed over the surface are areas corresponding in size and appearance with those upon the free surface, slightly elevated, firmer than the surrounding liver substance, showing distinct lobular markings; the centers of the lobules bile stained, the borders yellowish brown. The hepatic veins stand open, the surface of section is moist.

The microscopical examination is as follows: In this liver there are two different conditions which are separated, both macroscopically and microscopically. In certain areas, there is a comparatively large amount of well preserved liver tissue. Liver cells are normal. The nuclei stain well and the fine bile capillaries between the cells are injected with a greenish yellow bile pigment. These areas in the liver macroscopically appeared greenish. The liver cells contain no fat and the nuclei are relatively more numerous. There seems to have been a new formation of liver cells. The trabeculæ are wider than normal in places. The capillary bile ducts are dilated. No nuclear figures are found in the liver cells. The preserved liver tissue is chiefly about the portal spaces. The connective tissue in the portal spaces is increased. About the central veins everywhere the liver tissue is absent. In other sections which involve rather the less pigmented areas macroscopically the liver cells are in places

entirely absent or reduced to very small cell collections. One of the most marked features where the liver cells are absent is the presence of immense numbers of endothelial cells. These cells have an abundant dense cytoplasm, are often pigmented, are contained both within the capillaries and within the liver cell trabeculæ, and sometimes show vacuoles containing granular material or pigment. Where the liver cells are absent the tissue consists in a loose fibrous stroma containing these cells with some admixture of lymphoid cells. Here and there the endothelial cells contain lymphoid cells within their vacuoles. In many of these places there are a few scattered eosinophile leucocytes. In a few places only at the edge of the liver cell masses, the same process of cell disintegration, which is fully described in the other cases, is seen. The portal spaces and the tissue adjoining them everywhere contain immense numbers of the so-called newly formed bile ducts. In places, particularly where the liver cells have totally disappeared, these are very prominent and penetrate he tissue. They seem to be actively growing, he nuclei are numerous and nuclear figures in fair numbers are found in them. This case differs from the two following cases in the fact that here a destructive process analogous to that in the other cases, though not so extensive, has taken place. The period of destruction has ceased, or almost entirely so, and the dominant feature is a repair of the process, and regeneration. The regeneration of the liver tissue here is taking place in two ways: in one way by the direct formation of liver cells from other liver cells by division of nuclei. In the other, by a process similar to that of embryonic liver formation, by the formation of undifferentiated epithelial tissue similar in character to the bile ducts, from which the future liver cells will differentiate.

The enormous number of endothelial cells which are present is part of the process of repair, these cells being of a phagocytic character and engaged in the removal of the necrotic and broken down tissue.

Gall bladder, normal.

Kidneys, weight of both 400 gm.; capsule strips easily from a smooth surface; upon section, cortex 1 cm. in thickness, pale grayish red, showing yellow droplets within the tubular epithelium.

Adrenal glands, normal.

Bladder, normal.

Genitalia, tubules fail to thread.

Aorta, bile stained.

Cranium, sinuses and dura normal.

Brain, weight 1,390 gm.; upon section, somewhat softened and wet.

Spinal cord, not examined.

Bone marrow of the femur, red.

Bacteriological examination: cultures from the heart, lungs, spleen and liver show white and yellow colonies, microscopically cocci. Culture from the kidney sterile.

Case II. T. N., age thirty-two, single, a blacksmith, was admitted Dec. 10, 1904, to the Second Medical Service of the Boston City Hospital, which was temporarily in charge of the writer. The following history was obtained from the patient's sister: his family was a healthy one and no previous illnesses were remembered save measles and diphtheria in childhood. He used beer and whisky in moderation.

Present illness. — Was perfectly well till six days before entrance to the hospital when he had a severe headache, anorexia and general malaise. Next day he vomited several times, headache continued. He was up and about, and the following two days felt much better. Was constipated. No fever.

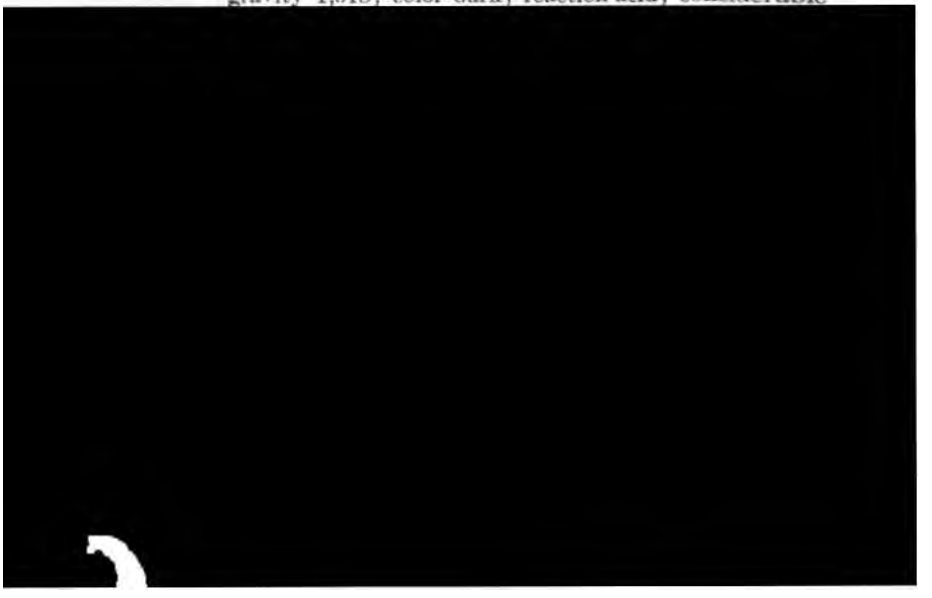
On the fourth day, mild jaundice was noted and some mental confusion. On the sixth day of his illness there was renewed nausea and vomiting and he came to the hospital on his physician's advice with the diagnosis of catarrhal jaundice. He walked to the hospital. At entrance he seemed irrational, was unable to recognize his own name, repeatedly jumped out of his chair when told to sit down, etc.

Physical examination, on the sixth day showed a well developed and nourished man, conjunctivæ and skin mildly jaundiced, reflexes normal, sordes present on lips and teeth, tongue dirty, protruded in median line, throat negative, glands not enlarged. Neck not tender or rigid. Pulse good, arteries elastic, heart and lungs normal.

The area of liver dullness was very unusual. The greater part of the normal area of dullness was tympanitic like the rest of the abdomen, and the only dull area in the liver region was about the size of one half the palm of the hand (2–2½ inches in diameter) just above the right costal margin in the anterior axillary line. The edge was not felt. No tenderness was present. The spleen was not felt, nor the area enlarged on percussion. The abdomen was lax, tympanitic and not tender. There was no edema, rigidity or paralysis.

The blood on the sixth day was as follows: hemoglobin, 78%; red cells, 5,120,000; white cells, 11,600.

The urine on the same day was 780 ccm., specific gravity 1,018; color dark; reaction acid; considerable



the urine and precipitation with alcohol, tyrosin was present, leucin absent as a crystalline sediment. This crude test was followed by an accurate analysis by the B-napthalin-sulphochlorid method and a little tyrosin and a very little leucin found.

Careful quantitative analyses were made to show the total nitrogen excretion and the proportion of nitrogen excreted as urea, ammonia and residual nitrogen. The following results were obtained (6th day, one day before death):

Total nitrogen excreted 9,874 gm., and of this 44%, or 4.32 gm., was excreted as urea (Folin's method); 25%, or 2.48 gm., was excreted as ammonia; 31%, or 3.17 gm., was excreted as residual nitrogen including uric acid.

The stools were clay colored and somewhat offensive and showed a great excess of fat as is usual in jaundice.

The patient was irrational and confused during the sixth day, and in the evening became violently delirious, fought, struggled and swore. An hour or two later, he became comatose with stertorous, irregular, rapid respiration, low muttering and feeble pulse and subsultus tendinum. Discharges were involuntary, conjunctivæ were injected and the face bathed in sweat. There was no further vomiting or any hemorrhage or eruption of any sort. There was no marked loss of weight. The temperature remained normal. The patient was confined in a camisole and sedatives and cardiac stimulants given.

The comatose condition continued through the night, and toward morning of the seventh day the extremities became rigid. General clonic convulsions began, and after a few moments of violent motion the contractions became tonic; the back arched and the body was supported by the back of the head and the

heels. This condition lasted for fifteen minutes. The pupils were of moderate size, the right slightly larger than the left and did not react to light. Later in the day the pupils were equal, but did not react to light. Kernig's sign and Babinski's reflex were present on both sides; the knee jerks were lively and ankle clonus present. The extremities remained rigid until death, the neck was rigid and retracted, the respirations slow and stertorous.

The jaundice became gradually more intense, reaching a deep lemon yellow color. The pulse gradually failed and the patient died on the afternoon of the seventh day of his illness and the third day after the appearance of jaundice.

The *autopsy* was performed by Drs. Mallory, Lewis and Duval of the Boston City Hospital eighteen hours after death.

Anatomical diagnosis.— Acute yellow atrophy of the liver; chronic fibrous pericarditis; acute bronchopneumonia; chronic fibrous pleuritis; chronic healed pulmonary tuberculosis of the lungs; chronic tuberculosis of lymph glands; infarctions in spleen; hemorrhagic gastritis; catarrhal enteritis; chronic general arteriosclerosis; coronary sclerosis.

Age thirty-two. Body length 173 cm.

Body of a well developed, well nourished male. Rigor mortis is extreme. Lividity is well marked over the whole of the body. It is particularly noticeable about the neck and face. Pupils equal 9 mm. There is no edema. Over the whole of the body, but particularly marked over the face, is a lemon yellow tint. The sclera and the dried secretions in the conjunctival sacs are bright lemon yellow in color.

Peritoneal cavity contains no free fluid. The serous surfaces throughout are somewhat dull. There are no

adhesions. The mesenteric nodes are rather prominent. The appendix is 18 cm. long, runs upward and outward along the outer body of the ascending colon, normal. Diaphragm reaches to the fourth rib on left side, third interspace on right side. The edge of the liver lies 4 cm. above the costal margin in the midclavicular line.

Pleural cavities are obliterated with rather firm fibrous adhesions. The pericardial cavity has 50 ccm. of lemon yellow fluid. The parietal pericardium is smooth. The epicardium shows over the right ventricle a dense white patch 1 x 2 cm. Over the folding margins of the auricles are a few fibrous tags.

Heart: weight, 330 gm. The muscle is firm, dark red and even in color. The *endocardium* and *valves* are normal. The coronary arteries show slight sclerosis.

Scharlach R. shows fat in small droplets within muscle fibers.

Lungs: weight, 1,385 gm., are expanded. The upper lobes of each side show on section gray collapsible surface, dripping clear fluid and air. Here and there toward apices a few calcareous nodules the size of a large pea. The right middle lobe and both lower lobes are expanded, feel nodular. Cut section shows a general light red surface marked with small dark red areas. These dark red areas are firm to the touch, and from the cut section oozes blood-tinged fluid, but air only from the lighter red areas.

Spleen: weight, 165 gm., capsule smooth. Section shows a grayish red, soft surface, much substance coming away on scraping with knife. Here and there, particularly toward the capsule, are dark red areas which are slightly firmer than the surrounding spleen substance.

Gastro-intestinal tract.— The stomach contains a pint

and one half of dark brownish-red fluid. The mucous membrane is white and slimy. Near the cardiac orifice and the posterior wall is a red area 2 mm. in diameter. The duodenum contains a moderate amount of greenish yellow mucus. From the common duct there can be squeezed some thick white mucus. The jejunum, ileum and colon sent unopened to the chemist.

Pancreas seems normal.

Liver: weight, 600 gm. In general, organ extremely flabby and can be folded completely on itself. Color, yellowish red. Capsule smooth. Margins thin and sharp. Section shows a general yellowish red surface marked with small points of intense red. Surface dry.

Scharlach R. shows much fat within the few remaining liver cells.

Microscopic examination of liver. — Sections of liver hardened in Zenker's fluid and stained with methylene blue and eosin. In these sections of liver examined with low power there are two main characteristics. In one there are extensive areas of hemorrhage around the hepatic veins. In some of these areas of hemorrhage the topography of the liver seems to be preserved. In other places the hemorrhages appear as blood lakes in the tissue. The liver cells are absent save in the immediate vicinity of the portal spaces. In these there are a small number of fatty, though otherwise normal appearing, liver cells. Between the central areas of hemorrhage and the periphery there is an indefinite tissue with few cells. In the portal spaces and extending between the remaining liver cells there is a dense cellular infiltration, chiefly lymphoid in character. The bile ducts are open and there are no apparent lesions either in arteries or veins, save that occasionally in some of the larger portal vessels there are recent red thrombi. Rarely are there seen structures correspond-

ing to the so-called newly formed bile ducts of cirrhosis.

In the other sections of the liver, the areas of hemorrhage are small and inconspicuous, and over large areas there are no liver cells whatever. The structure of the liver cannot be recognized, the main mass being apparently composed of granular-looking material in which there are large, often greenish colored, cells. With a high power, it is seen that in the hemorrhagic areas the blood is contained in masses corresponding to liver structure and separated by small spaces and fissures. Among the blood corpuscles there are unenucleated cells and occasionally imperfectly staining large cells of endothelial character often containing pigment. No liver cells or remains of liver cells or capillaries can be distinguished. The blood masses seem to correspond rather to the columns of liver cells than to the capillaries. In most of these places the red blood corpuscles seem to have coalesced. The single corpuscles are swollen and rounded.

Immediately outside of the area of hemorrhage is an area in which the cellular elements are large, rounded cells, often containing a small amount of yellowish or greenish pigment. The nuclei are variable in shape and stain intensely. Between these cells there is often some indefinite granular material, but no evidence of capillary walls or cell rows. The cytoplasm is granular. In a very few places there are masses which can be recognized as necrotic liver cell remnants. In these the cells seem to be changed into granular masses. The condition is different from that of the ordinary necrosis of liver cells. The cell masses lose their outline. They have not the sharp acidophilic character nor the refraction of ordinary necrotic liver cells.

In the other areas of the liver the change is more marked. In these, fragments of cells without nuclei

and with greenish pigment are numerous. Among these there are often larger cells which show active phagocytosis. One of the most striking conditions in this case is the complete absence of polynuclear leucocytes.

The condition in this liver is one of intense destruction of liver tissue. The condition is different from that which is seen in the ordinary necrosis of liver cells. The cells seem to soften and disappear by solution, leaving in some cases a more or less granular-looking mass behind. The condition affects also the capillaries of the liver. In the place of the liver tissue there is beginning to form a tissue composed chiefly of endothelial cells which in a few places show an active phagocytosis. The same process of tissue solution has affected the blood as there are no blood corpuscles in the most marked areas. In this softened tissue in places there has come a fresh influx of blood, the blood corpuscles lying chiefly in the spaces formerly occupied by the rows of liver cells. There is in no place any indication of regenerative process.

Kidneys: weight, 370 gm. Capsule strips readily from a smooth surface. Cortex well differentiated. Pyramids 7–10 mm. in thickness. Color grayish red. Glomeruli can be seen as gray points. Pyramids dark red. Blood vessels seen as reddish lines.

Scharlach R. shows fat in small droplets, large in quantity, within cells lining tubules of cortex and pyramids.

Adrenals are somewhat thin. The left adrenal seems lumpy. No gross lesions can be determined. Scharlach R. shows fat in central zone of cortex and in cells lining medullary portion.

Bladder and *genital organs* seem normal.

Aorta shows a moderate grade of fibrous sclerosis

running in longitudinal lines along the posterior wall.

Organs of neck.— The thyroid seems normal in size and consistency.

Lymph nodes.— The inguinal lymph nodes are somewhat enlarged. On section several of them show pinpoint yellowish-white firm spots. The mesenteric lymph nodes about the bile ducts and head of the pancreas are markedly enlarged and dark red on section. The post-peritoneal lymph nodes and the mesenteric lymph nodes in general are appreciably enlarged, on section dark red. Several of the mesenteric lymph nodes are calcareous.

Bone marrow.— The shaft and head of the right femur is rather gelatinous and alternates streaks of yellow with streaks of dark red.

Head.— Short, curly, dark brown hair. Scalp and calvarium of normal thickness. Dura non-adherent. Sinuses contain fluid blood. Pacchionian granulations moderate. Some little subpial edema. Vessels of pia injected. Circle of Willis normal.

Brain: weight, 1,380 gm. Rather firm in consistence. Convolutions of normal prominence. Ventricles, midbrain, pons, medulla and basal ganglia show nothing of special note.

Chemical examination of liver and intestinal contents. — The contents of the jejunum, ileum and colon were examined thoroughly and repeatedly for phosphorus without finding any.

The liver in this case was examined chemically by Dr. Carl S. Alsberg. It was slightly richer in water than is normally the case. It also contained a greater per cent of ether extract than is normally present, but as the liver weighed only 600 gm., the total ether extract of the entire liver was very much less than the ether

extract of a normal liver of 1,800 gm. In other words, while the relative amount of fat and lipoids was somewhat greater than normal, the absolute amount was very much less than normal. Furthermore, the nitrogen distribution was determined according to the method of Hauseman, Osborne's modification. The nitrogen precipitable by phosphotungstic acid was diminished and the nitrogen not precipitable by this reagent very markedly increased. These are conditions which very clearly show marked autolysis.

CASE III. M. C. C., age thirty-six, married, born in Ireland, a housewife, was admitted to the wards of the Boston City Hospital in the service of Dr. Francis H. Williams, on Dec. 1, 1905. Through his kindness the writer was permitted to examine and study this patient. The history was obtained from her physician and husband. Her family history was excellent. She had always been strong and well, no previous illnesses were remembered. Had used no alcohol and syphilis was denied. Two children had died soon after birth, of digestive disease; no miscarriages. Her digestion had been excellent and she had had no disease of the genital organs. There had been no recent infectious disease.

Present illness. — This began six days previous with severe headache, anorexia, malaise and general weakness, accompanied by a moderate flow of blood from the uterus. The last catamenia had ceased one week before; they had previously been very regular.

She had been in bed since the second day of the illness. There had been diffuse abdominal pain, occasional vomiting, and the bowels moved on the fifth day for the first time in several days. On the fifth day several mouthfuls of blood were vomited and slight jaundice was noticed for the first time. On the sixth day (the day of entrance to the hospital) the patient

became drowsy and lost consciousness for the first time. At entrance to the hospital she was semi-conscious, could only be roused by the strongest external stimuli,would not answer questions,rolled about the bed.

Physical examination showed a well developed, poorly nourished woman whose skin and conjunctivæ showed slight jaundice. The skin was very dry and scaling in several places on the abdomen; the tongue had a dry brown coat; the odor of the breath suggested acetone. The glands were not enlarged, neck not rigid or tender. The pulse was regular, slow, of good volume and tension. The heart was normal in size and the apex palpable and visible in the fifth space within the nipple line. The action was regular, both sounds were sharp and loud and the first sound reduplicated at the apex. A slight systolic murmur was heard at times at the apex and a cardio-respiratory murmur just to the left of the nipple. The lungs were normal. The abdomen was soft and lax without tenderness, masses or fluid. The *liver dullness* was difficult to determine accurately. There was tympany instead of flatness in the upper epigastrium and in the nipple line. The only definite area of dullness found was in the right axilla between the seventh rib and the costal margin extending only as far forward as the anterior axillary line. The spleen was not felt, nor the dullness found to be enlarged. The reflexes were normal. Kernig's and Babinski's sign were absent. The temperature was normal.

The blood on the sixth day was, hemoglobin, 60%; red cells, 6,720,000; white cells, 16,000.

The urine on the same day was passed involuntarily so that the twenty-four-hour amount could not be collected. A mixture of several catheter specimens showed the following characters:

Reaction acid; specific gravity, 1,028; color normal; albumin, a very slight trace; sugar absent. Albumose present; bile pigment present in small amount.

The sediment contained a few coarse, granular casts and renal cells with fat drops, a little free fat, leucocytes and squamous cells. Calcium oxalate crystals.

On evaporating the urine and precipitating with alcohol, both leucin and tyrosin were found present.

Quantitative analysis of the nitrogen excretion made by the writer showed that 69.2% was excreted as urea, 17.0% as ammonia; 13.8% as residual nitrogen including uric acid.

The stools were formed, of very dark color and contained a considerable amount of partially digested blood.

The treatment was essentially symptomatic. Purgation with calomel, with large enemata of salt solution; bromides for the restlessness, and heart stimulants. During the afternoon of the sixth day the patient's condition remained unchanged. She was very restless and noisy, tossing about in bed, rolling her head incessantly from side to side. There was no more vomiting. The patient occasionally coughed up a little blood-streaked sputum. A moderate bloody discharge from the uterus continued. The jaundice gradually deepened to a yellowish bronze color; the conjunctivæ were bright yellow. There were no hemorrhages into the skin. The bowels did not move again. Profound coma gradually developed. There were no convulsions, twitching, or rigidity. The temperature remained normal. The pulse became rapid and gradually failed. The patient died at noon on the seventh day of her illness and the second day after the appearance of jaundice.

The *autopsy* was performed by Drs. Mallory and

Graham of the Boston City Hospital, twenty-two hours after death.

Anatomical diagnosis:— Acute yellow atrophyof liver; acute parenchymatous nephritis; acute myocarditis; generalized icterus of skin, subcutaneous fat and serous membranes; multiple hemorrhages of lungs; multiple hemorrhages of mesentery; hemorrhages from gastric and intestinal mucous membranes and endometrium; congestion and edema of lungs; chronic pleuritis (bilateral); chronic perihepatitis; generalized passive congestion; myoma of uterus; biliary calculus; aortic arteriosclerosis (slight).

Body of a well developed, fairly nourished white woman, 159 cm. in length. Rigor slight in limbs, absent in neck muscles. Lividity of dependent parts marked. No edema. There is general icterus, skin surfaces a yellowish bronze in color, sclerotics bright yellow. Pupils equal, 0.5 cm. in diameter.

Peritoneal cavity. — Subcutaneous fat is of a salmon yellow color, its vessels filled with dark blood. Pectoral muscles dull red. On opening cavity all the serous membranes show yellowish discoloration. The mesentery shows numerous scattered punctate hemorrhages beneath the serosa. They occur in the region of the vasa intestini tenuis, especially along the line of attachment of mesentery to intestine and average 0.2–0.3 mm. in diameter. They are most numerous in the region of the small intestine. Appendix 7.5 cm. long, 0.6 cm. in diameter; direction downward and inward. Mesenteric lymph nodes not enlarged. Diaphragm, right fifth space, left sixth rib. No fluid.

Pleural cavities.— There are old fibrous adhesions over surfaces of left lung posteriorly; over surface of right lung anteriorly. No fluid.

Pericardial cavity. — Serosa smooth, glistening

throughout. Cavity contains about 25 ccm. of clear, dark yellow serous fluid.

Heart: weight, 245 gm. Pericardium smooth. Myocardium dull red, flabby; on section shows vaguely marked areas of opaque yellowish gray color; appears loose in texture. Endocardium shows yellowish discoloration. Coronary arteries not sclerosed. Valves negative.

Scharlach R. shows throughout the entire section the muscle fibers crowded with small fat droplets; large flat cells occur in the fibrous trabeculæ.

Lungs, right: middle lobe pinkish, crepitant; on section dry. Upper and lower lobes show slightly marked congestion and edema. Throughout both these lobes there are numerous scattered areas of hemorrhage averaging 0.5–1 cm. in diameter, which are most numerous in dependent portions. Anterior surfaces show tags of fibrous adhesions.

Left: Upper and lower lobes reddish in color, crepitant. Tags of fibrous adhesions posteriorly. On section, color bright red, surfaces are moist and show multiple hemorrhagic areas, especially posteriorly and inferiorly. There is no evidence of pus formation.

Spleen: weight, 100 gm. Capsule lax; on section, cut surfaces dull red in color, mottled with clearly defined grayish areas averaging 1 mm. in diameter. Trabeculæ distinct. Little pulp on scraping.

Gastro-intestinal tract. — Stomach shows adherent to mucosa a few small scattered, reddish-black masses appearing like old blood clots. Mucosa not perceptibly congested. The jejunum is empty except for a considerable quantity of reddish-black mucoid material with slight fecal odor. This material shows, microscopically, the presence of red blood cells in considerable

quantity. Similar material is found in the cecal region. No bleeding points found.

Pancreas. — Organ is softened in consistence. Cut surfaces moist and of edematous, semi-translucent appearance. Color dull grayish white. The spaces between the groups of gland acini are hemorrhagic.

Scharlach R., shows large fat droplets in the inter- and intra-acinar connective tissue. The parenchymal cells show a slight fatty change.

Liver: weight, 960 gm. On opening the abdominal cavity, liver appears to have fallen back from its normal position on to the posterior wall. It appears small; the anterior and superior surfaces of the right lobe are bound by a few old fibrous adhesions. Organ is soft in consistence, the capsule lax. The left lobe is of a peculiar ochre yellow color, dotted with dark-red points. Markings not distinct. The right lobe is mottled dark red to ochre yellow. On section, the left lobe shows same peculiar coloration as on external surface. Right lobe shows irregular areas of ochre yellow alternating with areas dark red in color. Dark red points are scattered thickly over cut surfaces. Normal markings cannot be made out. Gall bladder of normal size, contains a rounded olive-shaped calculus of " mulberry " appearance, 2.3 x 1.7 cm. It is filled with a clear viscous yellowish fluid containing a slight amount of whitish flocculent material. Cystic duct and common bile duct are patulous throughout, papilla of Vater appears normal. There is no evidence of cholecystitis.

Microscopic examination of the liver. — The case examined with the low power shows areas which correspond more or less well with the second case. In this there are areas of hemorrhage in the centers of many of the lobules. In places, chiefly in the centers of

the lobules, a disappearance of the liver tissue with the collection in these areas of endothelial cells. The liver cells are more extensively preserved. They are all of them intensely fatty, the fat being in very small granules. Certain of these fatty cells have lost their nuclei and appear to be necrotic. There are few polynuclear leucocytes, though more than in the preceding case. In some of the cell areas along with the large epithelioid there are cells chiefly of a plasma character belonging to the lymphoid series. No distinct cell phagocytosis is seen.

In this case also there is an extensive rapid destruction of liver cells with the same process of softening and disappearance as in the preceding case. The necrosis of the cells seems to have been preceded by an enormous formation of fat within them. In this case also the difference between this character of necrosis with liquefaction and the ordinary focal necrosis is striking. In neither of the cases is the necrosis focal. It is general and distributed all over the tissue with very slight difference in degree. In no place in this specimen have the liver cells totally disappeared.

Kidneys: weight, 210 gm. Organs are softened in consistency, stellate veins injected. In section, cortex 0.6 cm. in width; capsule very slightly adherent. The cortex and medullary rays are of an opaque light-yellow color; Malpighian corpuscles appear usually as fine red points, exceptionally as larger opaque yellowish gray granules. Extending into cortical region from the bases of the pyramid are radiating lines of translucent grayish appearance. Line of demarcation between cortex and pyramids is very distinct, the pyramids being dark red in color, their vessel prominent as dark red lines. Whole kidney appears engorged with blood.

Scharlach R. shows large and small fat droplets in

the epithelial cells of all the urinary tubules throughout their entire extent. The glomeruli show an occasional fine droplet.

Adrenals. — Both adrenals show marked injection of their vessels and appear slightly enlarged.

Bladder. — Mucosa is slightly bile tinged. Otherwise nothing remarkable.

Genital organs. — Tubes and ovaries appear normal. The uterus shows a rounded mass in the muscular wall of the upper fundus region which is grayish white in color, firm, cutting with considerable resistance. The endometrium of fundus region is dark red, slightly thickened. Adherent to it is a long chicken fat clot 0.5 cm. in diameter, extending to the internal os.

Aorta. — The lumbar portion of the vessel shows a few scattered pinpoint areas of slightly elevated, dull grayish appearance, a similar area larger in size, about the orifice of the celiac axis.

Head, not opened.

Case IV. M. McC., age twenty-four, single, housemaid, was admitted April 11, 1908, to the First Medical service of the Boston City Hospital in charge of the writer. The patient was comatose at entrance and the following history was obtained from her physicians, Dr. Merrick and Dr. McLaughlin, of Dorchester.

Previous history. — Her family was a healthy one. She remembered no previous illness. Her mental development was poor. She was considered feeble-minded, but was able to do simple routine work as a laundress. Thorough physical examination seven months ago on admission to an institution gave a normal result.

Six months ago she was delivered of a five months, anencephalic child. Her convalescence was normal; no history of syphilis was obtained and no evidence of

this disease was found in mother or child. She had never had a previous attack of jaundice.

Present illness. — Nine days before admission to the hospital her digestion was slightly disturbed and mild jaundice appeared. There was no abdominal pain. She had anorexia, vomited a few times and was somewhat weak and depressed. Physical examination on the third day showed nothing but the mild jaundice. The patient was given laxatives and a light diet and advised to keep quiet, and her illness was considered simple catarrhal jaundice. She did not take to her bed till the sixth day of the illness. There was some early variation in the depth of the jaundice, but from this time it increased rapidly and progressively. On the seventh day the patient was quite weak and on the eighth day mildly delirious. A few hemorrhagic papules appeared on the forehead, but there were no other signs of bleeding. There was no fever; the pulse was 96.

The possibility of acute liver atrophy was considered at this time and a careful examination of the hepatic area was made by the above named physicians. The upper border of liver dullness was found in the fifth right interspace and the lower border at the costal margin and the edge was just felt on deep inspiration; nothing abnormal was felt in the gall bladder region. The abdomen was soft and there was no abnormal tenderness. On the ninth day (the day of entrance to the hospital) she became comatose.

Physical examination on the tenth day showed a slender, fairly nourished woman in deep coma with the skin and conjunctivæ colored deep yellow; the pupils were equal and reacted well; the knee jerks were lively; no Babinski or Kernig signs were obtained. The lips were crusted and the teeth covered with blood-stained mucus. The pulse was 90, of good volume and tension.

The throat was negative, the tongue not protruded; the glands were not enlarged; the neck was not tender. There was occasional tonic spasm of the muscles of the extremities and neck. The heart was normal in size, the first sound was sharp with a suggestion of a presystolic roll and thrill at the apex. The lungs were clear. The abdomen was lax, soft, slightly tympanitic and not tender. The spleen was not felt. There was no ascites or edema of extremities.

The area of liver dullness was much diminished. The upper border was in the normal position in the fifth right interspace in the nipple line. The lower border ran approximately parallel to the right costal margin, *6 or 7 cm. above it*, and the liver dullness was thus reduced to a thin wedge running across the lower front of the right chest, tapering from 6 cm. in width in the anterior axillary line to 2 cm. in width in the midsternal line.

The *blood* on the tenth day was: hemoglobin, 75%; red cells, 6,100,000; white cells, 9,000. In a stained specimen the red cells showed slight achromia and little change in size or shape. There were no blasts. A differential count of the white cells showed: polynuclear leucocytes, 80%; lymphocytes, 12%; large mononuclear, 8%.

The *urine* was collected on the tenth day for twenty-four hours by means of catheterization every four hours, and showed the following characters:

Amount 400 ccm., color dark yellow; specific gravity 1,022. Reaction, strongly acid; albumin, a slight trace; sugar absent; bile pigment present in large amount; albumose and peptone present.

The sediment was deeply bile stained and contained many granular and epithelial casts; many renal cells, some fatty; considerable free fat, vaginal cells; no blood.

Leucin, much present; tyrosin, much present.

The examination of the urine for leucin and tyrosin was made by the B. napthalin sulphochlorid method.

Quantitative analyses were made showing the total nitrogen excretion in the urine and the proportion excreted as urea and ammonia (using the Kjeldahl and Folin methods). The following results were obtained: Total nitrogen excreted 4.575 gm. and of this 44.8%, or 2.05 gm., was excreted as urea; 12.6%, or 0.515 gm., as ammonia; 2.2%, or 0.101 gm., as uric acid; 7.8%, or 0.359 gm., as creatinine; 32.6%, or 1.57 gm., as residue.

The patient remained in deep coma, taking almost no food, not more than a few teaspoons of milk every hour. There was no further vomiting, or any external bleeding. Occasional tonic spasm of the muscles occurred, but no convulsions. On the day before death the temperature rose to 100.6° and the pulse to 125. The pulse gradually failed in strength and the patient died on the morning of the eleventh day of her illness, the eleventh day after the appearance of the jaundice and the third day after the appearance of the severe cerebral symptoms.

The autopsy was performed three hours post-mortem by Drs. Mallory and Rhea of the Boston City Hospital.

ANATOMICAL DIAGNOSIS.

Acute yellow atrophy of the liver; icterus (general); bronchopneumonia (right lower); fatty degeneration of kidney; subperitoneal hemorrhages (multiple); subpleural hemorrhages (visceral and parietal) (multiple); subpericardial hemorrhages (multiple); congestion and edema of lungs (lower lobe posteriorly); laceration of cervix (bilateral); corpus hemorrhagicum; acne (back) icterus of dura.

Age, twenty-four years. Body, length, 149 cm.

Body is that of a fairly well developed and fairly well nourished white female. Body, length 149 cm. Rigor mortis is present. There is some lividity of the dependent parts, most marked throughout the lower back. Pupils are 5 mm. and equal. There is no edema. The skin is everywhere dry and is of a very deep yellowish color. This yellowish discoloration is least marked on the hands and the feet, especially on the palmar surfaces of the hands. The conjunctivæ are very deep yellow. Over both cheeks and eyelids are numerous discrete and confluent, light brownish areas which vary from 2 mm. to 6 mm. in diameter. The hair of the eyebrows is very soft and silky. Over the upper part of the back are several discrete, slightly elevated, dark brownish red areas which stand up slightly above the surrounding skin. The centers of some of these areas show small pustules. The external orifices are normal. The abdominal fat measures 3 cm. in thickness. It is firm and of a very bright yellow color.

Peritoneal cavity. — The peritoneum is for the most part smooth and glistening throughout. The underlying tissues are of a light yellow color. The ileocecal fossa is very distinct and measures 2 cm. in depth. The distal 2 cm. of the vermiform appendix rests in this fossa, entering it behind the fold of the peritoneum which forms the right border of the ileocecal fossa. The appendix measures 5 cm. in length, is free from adhesions and has a mesentery to within 6 mm. of its tip. Both iliac fossæ show numerous small, discrete, sharply outlined, oval and round, deep red areas which shine through the peritoneum. Beneath the peritoneum, covering the mesentery and the retroperitoneal tissues, are numerous discrete, round and oval, bright red areas. Similar areas are seen beneath the peritoneum covering the mesentery of the ascending

and transverse colons. The mesenteric lymph nodes are not increased in size or consistence. On section they are pale. Diaphragm, left fifth rib, right fifth space.

Pleural cavities. — They are free from adhesions. The surfaces are generally smooth and glistening. Beneath the pleura covering the diaphragm on each side are several small, discrete, dark red areas, similar to those seen beneath the peritoneum.

Pericardial cavity. — The pericardial fluid is normal in amount and shows marked yellowish discoloration.

Heart. — Weight 180 gm. The width of the right auricle at its mid-portion is 12 cm. The depth of the right ventricle is 6 cm. The width of the left auricle at its central portion is 11 cm. The depth of the left ventricle is 7 cm. Just beneath the pericardium covering the left ventricle, most marked in the areas where the pericardial fat is in greatest abundance, are several discrete, round and oval, dark red areas, similar to those seen beneath the pleura and beneath the peritoneum. The myocardium is firm and of a uniform slightly yellowish color. This yellowish discoloration is most marked in the immediate vicinity of the larger blood vessels. The endocardium is smooth and glistening throughout. In none of the heart cavities is there any clotted blood except a very small amount between the trabeculæ in the region of the tip of the left ventricle. There is a moderate amount of fluid blood in both ventricles.

Measurements: tricuspid valve, 9 cm.; pulmonary valve, 6 cm.; mitral valve, 8.5 cm.; aortic valve, 5.5 cm.

Lungs. — Left: Just beneath the pleura in the region of the apex, both anteriorly and laterally, are numerous small, discrete, deeply injected areas which are irreg-

ularly oval to round in shape. These areas extend a very short distance into the underlying lung substance. On section the upper lobe is generally of a light salmon pink color. In its lower anterior portion there are several discrete and confluent, dark red areas which vary from 2 mm. to 3 cm. in diameter. In these areas the lung is less crepitant than elsewhere. On pressure a very dark blood-stained fluid escapes from them. The remainder of the lung is of a light salmon pink color except in the lower posterior portion of the lower lobe, which is generally a dark red in color, and from its cut surface a considerable amount of blood-stained fluid escapes.

Right: In the anterior lower central portion of the lower lobe there is a slightly elevated, sharply outlined, firm area 4 cm. in diameter. On section this stands up somewhat above the surrounding lung tissue, and on pressure numerous pinpoint, light grayish drops of fluid exude. The remainder of the lung is crepitant, slightly less so in the posterior portion, where the lung substance generally is of a dark red color, and a considerable amount of blood-stained fluid escapes. The upper lobe is light salmon pink in color. It is crepitant throughout.

Spleen. — Weight 110 gm. The surface is smooth. On section the pulp is light brownish red in color and of normal consistence. The Malpighian bodies are distinctly visible as small, grayish points. The vessels and trabeculæ are just visible.

Gastro-intestinal tract.— The stomach contains a small amount of undigested liquid food. Its mucous membrane is normal. The small intestine contains thin, bile-stained fecal material. Its mucous membrane is normal. The large intestine contains in its upper portion a small amount of thin bile-stained fluid;

in its lower portion a moderate amount of firm, dark brown, fecal material. The mucous membrane of the intestinal tract generally is distinctly discolored yellow.

Pancreas. — Normal.

Liver. — Weight 595 gm. Upon opening the abdominal cavity there is no part of the liver visible, it being situated entirely behind the ribs. At the central portion of the right lobe the lower margin of the liver reaches to within 5 cm. of the costal margin. When the liver is removed there is quite a marked tendency for the organ to collapse. Save at the extreme tip, the left lobe can be easily rolled up like a scroll. When rested upon the right lobe with the left lobe pointed upward, this latter portion tends to collapse over the right lobe. Generally the external surface of the liver is light brownish in color and its capsule is thrown into very delicate folds, though there are certain firm areas which are elevated, sharply demarcated from the surrounding liver substance, of deep yellowish color and consist of discrete and confluent areas. The largest is situated at the extreme tip of the left lobe. This area is 5.5 cm. long and 6 cm. broad at its base. Its extreme tip consists of a diffluent area. This diffluent area extends to the right along the course of the upper lobe for 2.5 cm. The remaining 3 cm. of the elevated area at the tip of the left lobe is made up of discrete, elevated, yellowish nodules between which the liver substance is slightly depressed and of a light yellowish red color. There is a discrete, firm, elevated area in the dome of the left lobe. This area measures 4.5 cm. by 6 cm. In general it is similar to the area described above in the extreme tip of the left lobe. Elsewhere throughout the surface there are small, discrete, elevated, firm yellowish areas. On section the liver shows the following picture: The two large elevated

areas described above, the one situated in the extreme tip of the right lobe and the other in the central portion of the dome of the right lobe, extend down entirely through the liver substance and are quite sharply demarkated from the surrounding parenchyma. They are made up of large confluent and small discrete, distinctly elevated, firm, yellowish areas, the former in their central portion, the latter about their periphery. They are much firmer than the surrounding liver substance and are quite friable. The remainder of the liver is flabby and on section is generally very light brown in color with small, narrow, band-like, pale areas, which interlace, dividing the liver into distinct lobular-like areas. While the elevated yellowish areas are generally confined to the two larger areas described above, there are a few small areas of similar character throughout the remainder of the liver substance. The gall bladder and its ducts are opened *in situ*. The gall bladder contains a small amount of thin, yellowish bile. The bile ducts are patent. The ampulla of Vater is normal. Bile escapes into the duodenum upon pressure of the common bile duct, or the gall bladder.

Kidneys. — Weight 260 gm. On section the cortex is of a pale, distinctly yellowish color and is very sharply demarcated from the pyramids, which are a light brownish red in color. The blood vessels in the cortex and pyramids are slightly injected. Malpighian bodies are distinctly visible as small glistening points.

Adrenals. — Normal.

Bladder. — Is contracted. It contains a small amount of dark-colored urine. The mucous membrane of the bladder is deeply bile stained.

Genital organs. — The cervix is smooth and glistening. Its mucous membrane is light yellowish in color.

The cervix shows a transverse, bilateral tear. The uterus measures 7.5 cm. long and 1.5 cm. broad at the external os, 1 cm. broad at the internal os and 4 cm. broad at the fundus, between the cornu. The left ovary is normal. The right ovary is slightly increased in size and contains a sharply demarcated, very dark red area 8 mm. in diameter.

Aorta. — It is generally of a deep yellowish color. At the bifurcation it is 2.5 cm. in diameter; at its mid-portion 3.5 cm.; at the lower portion of the descending arch 4 cm. in width. In its lower third it shows a few linear, slightly elevated, slightly yellowish patches.

Organs of neck. — Normal.

Bone marrow. — The bone marrow of the femur is soft, made up of dark red, granular areas embedded in fat. The ribs show a rather small amount of bone marrow. The bony framework of the medulla of the ribs is rather prominent. The bone marrow of the vertebra is light red in color.

Spinal cord. — The subdural fat is distinctly bile stained. The dura is not adherent. On section the markings of the cord are distinct. There are no gross pathological lesions demonstrable.

Head: weight, brain 1,270 gm. Head is covered by a thick growth of long brown hair. The calvarium is negative. The dura shows a decided light orange color and is moderately adherent to the calvarium. On section the brain is apparently normal.

Middle ears. — Normal.

Microscopic Examination.— The heart shows slight fatty degeneration. The spleen, pancreas, adrenal, gastro-intestinal tract and central nervous system are practically normal. The kidney shows very extreme fatty degeneration of tubules of all types. The glomeruli show no changes.

Liver. — Sections were taken from numerous regions. All show very marked degeneration; those from the firmer, yellow, elevated areas, noted at autopsy, show less marked changes. The general picture in the section from the more normal regions shows large and small islands of liver cells widely separated by a tissue containing only blood spaces and cells of inflammatory origin. The large groups of liver cells, in some instances, show a lobular arrangement. The smaller groups show no trace of normal structure. All of the liver cells show marked changes. There is an increase in size with marked vacuolation, and at the periphery of the groups the vacuolation is extreme and the shapes assumed are irregular and often grotesque. The bile capillaries are prominent and filled either with a densely stained eosin material, or inspissated bile. In the surrounding tissue no trace of liver cells is to be found. There are many large, mononuclear cells, some of which are pigmented yellow, while others are phagocytic, and numerous cells of the lymphoid series. These cells lie in spaces between injected blood spaces which evidently correspond to the sinusoids of the liver.

In the regions of most marked destruction of the liver tissue, there are only a few small groups of cells recognizable as liver cells. There remain only marked injected blood spaces, probably corresponding to the sinusoids. Between the blood spaces there are many pigmented and phagocytic mononuclear cells. In places there seems to be an increase of connective tissue, but this is not confirmed by the connective tissue stain. Within small groups of liver cells there are numerous polymorphonuclear leucocytes. None of the liver cells show the dense hyaline change of the protoplasm seen in other forms of degeneration. Everywhere throughout these portions of the liver,

there are many branching bile ducts, in which many evidences of direct nuclear division can be found. Mitoses were not found in the liver cells, though some cells have a denser basic staining, compact protoplasm like that of cells found in regenerating liver tissue. No definite hemorrhages are present. The Scharlach R. stain for fat shows that the vacuolated liver cells contain fat.

This case presents the same general conditions which have been described in the preceding cases. The stage of the process is earlier than that of the first case and probably later than either the second or third case, as regeneration is taking place, at least from the bile ducts.

CHEMICAL EXAMINATION.—The following tissues were sent to Dr. Carl L. Alsberg, of the Harvard Medical School, for chemical examination: Heart, heart's blood, lung, spleen, liver, kidney, adrenal, intestinal contents. A part of the results of chemical analysis of the liver are given. The other analyses were not completed in time to be included in this paper. They will be reported later.

The liver was examined chemically to determine the distribution of nitrogen according to the method of Hauseman. Osborne's modification. (*Journal of the American Chemical Society*, 1903, xxv, 323.) The analyses were made in duplicate. The per cent of the different forms of nitrogen is as follows (the nitrogen under the fifth heading does not come under the heading of monamino, diamino or amid nitrogen. Osborne simply reports it as nitrogen in the Mg O_2H_2 precipitate):

Liver analysis. — Total nitrogen, 2.66%; amid nitrogen, 0.18%; monamino nitrogen, 1.62%; diamino nitrogen, 0.55%; nitrogen in the precipitate obtained

by digestion with acid and addition of excess of Mg O_2 H_2, 0.31%.

The diamino nitrogen in this case is not so low as is sometimes found in cases of autolysis.

CLINICAL SUMMARY OF THESE FOUR CASES.

Occurrence. — Two of our patients were men and two women. The disease is, however, almost twice as common in women as in men, the usual proportion of incidence being 8 women to 5 men. (Quincke.) The patients were of an age (twenty-three, twenty-four, thirty-two, thirty-six) when the disease most commonly appears. All four of our cases developed in the winter time, but season is not considered an important factor.

Etiology. — The preliminary stages were like simple catarrhal or other benign jaundice. Minkowsky has expressed the opinion that the difference between simple benign jaundice and the rapidly fatal type is simply one of degree of intensity of action of the same or similar factors upon the same tissue, and that no sharp distinction can be drawn. Every jaundice, no matter what its cause, may lead to hepatic insufficiency and end in acute atrophy, and the tendency to the severe form of the disease depends on the lack of resistance of the organism as well as upon the intensity of the effect of the poison.

It is, however, fair to suppose that the sudden outburst of severe symptoms is not a sign of the entrance of some new causal factor into a simple case; but in reality the chemical changes which

produce these symptoms have been preparing for some time, as in uremia and diabetic coma, and the illness has been actually grave from the start.

Certain infections, especially syphilis, play a part in etiology. One of our patients was in the second stage of syphilis when the acute atrophy occurred. This is fairly common. Senator has collected 20 such cases. The question has been raised whether the syphilitic poison or the mercury used in its treatment was the cause of the liver necrosis.

There is no definite evidence in our cases of the development of poisons from ordinary food or of the eating of poisonous substances, such as mushrooms, or of acute alcoholism. A careful analysis of the intestinal contents and liver of two of our cases showed that phosphorus was absent.

The direct importance of bacteria in this disease is very doubtful. Cultures in our cases were either sterile or apparently without significance as is usually the case.

The disease in our patients appeared in otherwise healthy livers, as usually happens, though it may be superimposed on other liver disease, such as cirrhosis, bile stasis and fatty degeneration.

The question of etiology will be more fully discussed under the heading, "Nature of the Disease."

Pathological anatomy. — The liver in all the cases showed a characteristic reduction to one

half or almost one third the normal size and weight. The normal weight of the liver is 1,500 to 1,800 gm. In our cases it was 730, 600, 960 and 595 gm. respectively. It was flaccid, flattened, folded, and dropped backward unless held by adhesions as in the third case. The cut surface was yellowish red or yellow, mottled with or alternating with large or small red areas. The markings were usually indistinct. The yellow color is not due to fatty degeneration, for this is not the chief change, and in fact fat may be almost entirely absent. Taylor found in a liver which he examined that there was no increase of fat over the normal amount. The chemical analysis of the liver in our second case showed that the amount of fat and lipoids was very much less than normal. The yellow color is due chiefly if not wholly to bilirubin.

The condition is one of intense destruction of the liver tissue different in character from the ordinary necrosis of liver cells. The cells seem to soften and disappear almost entirely by solution, leaving behind connective tissue enclosing endothelial cells and a more or less granular material. The cell masses lose their outline, and have not the sharp acidophilic character nor the refraction of ordinary necrotic liver cells.

In none of the cases was the necrosis focal. It was general and distributed all over the tissue with very slight differences in degree. In the third case the necrosis of the cells seems to have been preceded by an enormous formation of fat

within them. Fat was almost entirely absent in the other cases.

The first case differed from the others in the fact that it was of somewhat longer duration, fifteen days instead of seven or eleven, and the destructive process was not so extensive and had almost or entirely ceased. The dominant feature was a regeneration to replace the destruction of liver cells. The regeneration of liver tissue was taking place in two ways. In one way by the direct formation of liver cells from other liver cells by division of nuclei, in the other by a process similar to that of embryonic liver formation by the development of undifferentiated epithelial tissue similar in character to the bile ducts and from which the future liver cells develop. The enormous number of epithelial cells which were present were assisting in the process of repair, these cells being phagocytic and engaged in the removal of necrotic and broken down tissue. The presence of bile in the capillaries might be taken as an indication of the very great activity of the remaining liver cells.

This case is especially interesting from its relation to other diseases of the liver. It forms a transition stage in acute and subacute forms of hepatic cirrhosis. Had the destruction of liver tissue not been so profound this case might have developed into some one of the peculiar forms of cirrhosis with atypical lobulation.

In the fourth case also regeneration of liver tissue was in progress to replace destroyed liver

cells. The stage of the process is earlier than in the first case, probably because the process of repair of the liver was cut short by the death of the patient at an earlier time (in eleven days instead of fifteen days). The regeneration of liver cells was taking place as in the first case from the epithelium of the bile ducts.

In the two cases (No. 2 and No. 3) which did not survive beyond one week, no evidence of any attempt at regeneration of liver tissue was found.

The four cases of acute yellow atrophy taken as a whole show a pathological process which consists in a peculiar autolytic destruction of liver tissue. There is an absence of leucocytosis; either the toxin or the necrosed tissue repels the polynuclear leucocytes. Their place is taken by enormous numbers of endothelial phagocytic cells which are probably formed locally. With the cessation of the process of destruction there takes place a rapid regeneration which comes both directly and indirectly. The hemorrhage, so prominent in the second case, seems to have rather the character of a secondary process; it is unusual, and does not form an essential element in the condition. Whether the blood undergoes autolysis at the same time with the liver tissue is uncertain.

The changes in the heart and kidney were those usually found, namely, fatty infiltration and granular degeneration of the epithelium of the kidney and of the heart muscle.

The spleen was soft but not enlarged, as is the rule; in fact the spleen in our three cases was rather small. The normal weight is from 130 to 250 gm. and in our four cases was 100, 165, 100 and 110 gm. respectively.

Ecchymoses were found in or under the serous or mucous membranes in all four cases. In the liver in one case, bowel in two cases, stomach in two cases, mesentery in two cases, uterus in one case, lung in two cases, heart in one case.

Nature of symptoms. — The course of the disease in these patients may be divided into a prodromal stage of six to twelve days, and a short and severe second stage, beginning with the onset of cerebral symptoms and lasting one to three days; the total duration of the illness was fifteen days in one case, eleven days in another and seven days in two others.

In the prodromal stage nothing characteristic appears. All the cases were considered simple catarrhal jaundice by the attending physician until the cerebral symptoms occurred. In all the cases there was severe headache and early gastric symptoms. Early hemorrhages from the stomach and uterus occurred in one case. This is unusual in time. Hemorrhages occur in over one half of the reported cases but are usually limited to the last two or three days of the disease.

Jaundice was a fairly early symptom in all these cases, appearing one to four days after the first symptoms of digestive disturbance.

The stools were clay-colored and fatty in three of the cases, and in the third dark through the presence of blood.

Enlargement of the liver was noted clearly in the first and fourth cases where the patients were under observation previous to and during the whole illness. The other two cases came under observation when the liver was already atrophic.

The second stage was ushered in by cerebral symptoms, mental confusion, irrationality, drowsiness, beginning coma, and progressed rapidly to active delirium and finally deep coma. Severe convulsive seizures occurred in two of our cases. They have been present in about one third of the reported cases in adults. Constipation was marked and nausea and vomiting frequent. The jaundice became very pronounced from deep yellow to bronze or orange color.

The spleen was not enlarged in any of our cases. In about two thirds of the reported cases splenic enlargement was found.

Hemorrhage is a prominent symptom. Hematemesis in small amounts is the most frequent form and occurred in all the patients but one. Hemorrhages into the skin, the next most frequent form, was found in only one of our cases. Hemorrhage from the bowel occurred once and uterine hemorrhage once. One case had bloody sputum.

No fever occurred except an ante-mortem rise in the last twelve hours in the first and fourth cases. No especial slowing of the pulse was noted

in the first stage. As the patients became weaker the pulse grew rapid and weak also.

The examination of the blood was interesting. The hemoglobin was moderately reduced, 60% to 80%, and the white corpuscles moderately increased, 9,000, 12,600, 11,600 and 16,000. The most striking feature was the increase in the number of red cells, 6,640,000, 5,120,000, 6,720,000 and 6,150,000, respectively. This is a striking condition in a disease accompanied by hemorrhages. The same condition is seen in phosphorus poisoning. It apparently is not due to simple concentration of the blood through vomiting of liquid, as the count was highest in the case in which the least vomiting occurred. If it were due to persistent starvation of fluids we should expect to find it more frequently in similar delirious patients.

The most striking feature of the physical examination was the rapid and almost complete disappearance of the liver dullness in the last few days of the illness, due to the softening, folding and dropping backward of the atrophic liver. All that remained in three of these cases was a small area of dullness, 2 to 3 in. in diameter in the right axilla and in the fourth a narrow strip, one or two inches wide, running across the lower right chest. In the first and fourth where the whole course of illness could be followed, the contrast and change from a slightly enlarged and easily palpable liver to the condition of extreme atrophy was especially striking. Hepatic

tenderness which, according to Reiss, persists even in coma, was conspicuous by its absence.

No enlargement of the spleen was found. This is unusual.

The only skin eruption was a few hemorrhagic papules appearing in the second stage in the fourth case and there was no apparent change in cutaneous sensation.

The general nutrition was only moderately affected. This is unquestionably due to the short duration of the illness.

The urine in all the patients was decreased and contained bile pigments, also small amounts of albumin and a considerable variety of casts and fatty epithelium. The most interesting changes were those which resulted from the hepatic insufficiency and perversions of metabolism, and were indicated by the change in the excretion of urea, the relative diminution of urea and increase of ammonia, and the appearance in the urine of other bodies not normally present, such as leucin, tyrosin and albumose.

It might be expected that the excretion of nitrogen would be increased by the rapid destruction of liver tissue, and it would have been very interesting to have determined this matter by an accurate observation of the ingestion and excretion of nitrogen for several days in succession. An accurate metabolism experiment was practically impossible from the nature of the illness, associated with delirium, frequent vomiting and involuntary discharges. In three of the

cases, however, the change in the character of the nitrogen compounds found in the twenty-four-hour urine (collected by repeated catheterization) was definitely determined and was very characteristic.

The total nitrogen excretion in cases I and II, 7.4 and 9.8 gm. respectively, was apparently somewhat high on practically a starvation diet with vomiting and poor absorption of food.

In all the cases the excretion of urea was relatively much diminished, and the excretion of ammonia and other nitrogenous substances (classed as residue) was relatively greatly increased as a result of high-grade liver insufficiency and other changes in metabolism. This is shown in the following table:

These changes in the urine show considerable variation in the four cases. This is undoubtedly to be explained by the different degrees of damage to the liver.

In two cases the urine was tested for leucin and tyrosin only by examination of the crystalline sediment after evaporation to 1-10 volume and precipitation with alcohol. Leucin and tyrosin were both present in one case and both absent in the other. In two cases the urine was tested by the much more accurate B-napthalin-sulphochlorid method, and leucin and tyrosin were both present in each case. The excretion of these substances does not measure the amount formed. Both are difficultly soluble and much may be left in the liver.

Albumose was present in two cases.

	Urine amount ccm.	Total nitrogen (gm. per cent).	Urea nitrogen (gm. per cent).	NH_3 nitrogen (gm, per cent.)	Total nitrogen.	Urea, nitrogen.	NH_3 nitrogen.	Uric acid nitrogen.	Residue nitrogen.
Case I,	960	7.40	4.64	1.61	100%	62%	22.9%	1.6%	13.5%
Case II,	780	9.87	4.32	2.48	100%	44%	25.%		31.0%
Case III,					100%*	69.2%	17.%		13.8%
Case IV,	400	4.575	2.05	0.515	100%	44.8%	12.6%	2.2%	32.6%
Normal,	1,500				100%	84–87%	2–5%	1–3%	7–10%

* The percentages in this case are based upon a sample including almost the whole twenty-four-hour amount of urine; the total amount could not be collected.

The purin bases (Salkowski method) were determined quantitatively in the first and fourth cases and were not found increased as they often are from increased nuclear destruction, or lack of decomposition of uric acid.

Prognosis. — The disease is a very fatal one, and the outlook is worse the earlier the cerebral symptoms appear. The prognosis in the individual case depends upon the degree of disturbance of the central nervous system. Rapid decrease in liver area, and leucin and tyrosin in the urine usually precede death by only a few days. The presence of hemorrhages is a very unfavorable sign. The state of the kidneys is very important in prognosis. Free diuresis is very necessary to avoid an accumulation of toxic products of metabolism. The grave symptoms of the second stage usually appear simultaneously with a marked reduction in the amount of urine and a great decrease in the nitrogen excretion, which must be considered a sign of retention of poisonous substances in the body.

The possibility of recovery from this disease cannot at present be denied. There is no reason why the injury to the liver should not stop before the liver tissue has been completely destroyed, and when the process of destruction stops rapid regeneration occurs. This regeneration may conceivably go on till more or less complete restoration of liver function and general health is reached.

Our first case showed an extensive process of regeneration of liver tissue and the fourth case a

considerable degree of regeneration. The amount of regeneration of liver tissue bears a close relation to the rapidity and violence of the toxemia in our four cases. The longer the patient survived his toxemia, the greater the liver regeneration; in the first case, fifteen days' illness, extensive regeneration; in the fourth case, eleven days' illness, moderate regeneration; in the second and third cases, seven days' illness, no regeneration of liver tissue. Other fatal cases in the literature have shown these same regenerative changes, and a considerable number of cases of recovery, now between 20 and 30, have been collected and reported by Wirsung, Senator, von Jaksch, Albu and others.

Diagnosis.— Early diagnosis from a practical clinical standpoint seems almost impossible. Simple benign jaundice is so common and acute atrophy of the liver so rare, that to subject every simple case to elaborate quantitative analyses to determine whether or not it seemed likely to develop acute atrophy of the liver, would be an enormous labor which would bear little fruit.

From a practical standpoint the nervous symptoms were the first guide to the diagnosis. Any unusual disturbances of the general nervous system appearing in acute jaundice should rouse our suspicions of this serious disease. The correct diagnosis was not made, or even suspected, in any of our cases, until the appearance of the second stage.

The decrease in the area of liver dullness which was so striking and characteristic in all the cases did not appear in the two cases which were under continuous observation till the second stage of the disease within two or three days, at most, before death. Even the presence of adhesions in the third case between the upper surface of the liver and the diaphragm did not prevent the reduction in the area of dullness, though under some circumstances they do obscure the evidence of decrease in size.

The presence of leucin and tyrosin in the urine formerly was considered pathognomonic of the disease. We know now, however, that they may occur in the urine in any condition in which there is much destruction of tissue in the body, but in no other condition in so large amount as is present in acute liver atrophy. They have a certain value in diagnosis, but this has been greatly exaggerated, in my opinion, and is in reality very small from a practical point of view. Their appearance is usually late in the disease, not before the second stage.

The simple methods of detection are unreliable and the accurate methods elaborate and long. If an accurate test is made in the second stage of the disease, as it usually is, it can rarely be completed before the patient dies and has no part in the antemortem diagnosis. The simplest method of detection is examination of the urinary sediment after evaporation of the urine to 1-10 its volume and the addition of alcohol. This microscopical diagnosis

by means of crystals is a rough and unreliable method and should always be confirmed by chemical tests. Tyrosin needles must not be confused with bilirubin or calcium phosphate crystals. Leucin spheres must be distinguished from urates. This is often difficult and it is wise to remove the urates by precipitation with lead acetate and remove the latter by hydrogen sulphide before examining the urine for crystals.

No simple chemical test had been devised at the time the earlier cases were studied, and the best present chemical methods of analysis for leucin and tyrosin are only qualitative and only moderately delicate; a decided disturbance of liver metabolism may occur without causing their appearance in amount sufficient for detection. The methods of analysis are much too elaborate for the clinician. They require the experience of an expert chemist and their description is outside the scope of this paper. They will be found in the textbooks on biological chemistry. One of the best ways of examination is by the B-naphthalin-sulphochlorid method which was used in our later cases, Nos. 2 and 4.

Estimation of the relative amounts of the nitrogenous substances excreted in the urine, such as urea, ammonia and the residual nitrogen, is of much more value in diagnosis. When no peptones are present in the urine the residual nitrogen is made up chiefly of amino acids, such as alanin, cystin, etc., in addition to leucin and tyrosin. All these substances are intermediate products of

nitrogenous metabolism, and the other amino acids have an equal significance with leucin and tyrosin in this disease. The exact quantitative estimation of this residual nitrogen, chiefly composed of amino acids, is a better way of measuring the disturbance of liver metabolism than a test for the presence of leucin and tyrosin by a rough and unreliable microscopic examination or by a merely qualitative method which is complicated, but not very delicate.

Even the disturbance of liver function, which we assume to be shown by the increased excretion of ammonia and a lessened excretion of urea in the urine, must be used with caution as a diagnostic sign on account of its variability and dependence on other factors, such as acidosis.

The actual character of the nitrogen excretion in these cases, as well as the presence or absence of leucin and tyrosin, were determined by analyses made *after the death of the patients* on urine previously collected, and while very interesting and important *they played no part in the ante-mortem diagnosis. This will usually be the case.*

In two cases the urine was tested for leucin and tyrosin only by examination of the crystalline sediment after evaporation to 1-10 volume and precipitation with alcohol. Leucin and tyrosin were both present in one case and both absent in the other. In two cases the urine was tested by the much more accurate B-napthalin-sulphochlorid method, and leucin and tyrosin were both present in each case.

The presence in the urine of oxy-acids derived from the amido acids, of lactic acid, of albumoses, and of purin bodies from the increased destruction of nuclei cannot be said to have any special diagnostic significance.

Severe cerebral symptoms appearing with jaundice have been termed *icterus gravis*. This condition may be present in quite a variety of pathological conditions, chiefly severe acute infections, such as pneumonia, sepsis, typhoid, malaria, peritonitis, etc. They can usually be excluded by the absence of fever, the intensity of the jaundice, the very small area of liver dullness, the urinary changes, and the absence of specific signs, such as changes in the lungs (pneumonia) or the blood (malaria, typhoid).

The diagnosis from acute phosphorus poisoning may be peculiarly difficult; fortunately it rarely has to be made in this country. The illness is of very short duration, the jaundice usually less marked, and the hemorrhages larger.

When the course of the illness is fairly typical, as it was in our four cases, any one having the clinical picture of the disease well in mind would have little difficulty in diagnosis when the second stage was reached. The diagnosis is much more likely to be missed because the disease is not considered on account of its rarity, rather than because it was carefully considered and then ruled out.

Treatment in our cases, and of the disease in general, is most discouraging and unsatisfactory.

The results of treatment seem trifling and hopelessly ineffective in the face of so violent and fatal a malady. Something may possibly be expected of treatment in the prodromal stage which is practically that of catarrhal jaundice. Our first effort should be to remove any harmful material from the digestive tract by calomel or salines. Laxatives also stimulate peristalsis in the bile passages and help to empty them. Plenty of drinking water will help to dilute the bile and lessen its consistency, and the absorption of water from the bowels will help to dilute those substances which might damage the liver in their passage through it. Its value as a diuretic and means of washing out poisonous substances from the body is very important. More active diuretics, caffein, diuretin, are occasionally useful.

We also try to lessen the work of the diseased organ by an appropriate diet; limit fats and give them only in emulsion (milk); carbohydrates, the principal food, are given in easily digestible form.

In the second stage the same principle of removing poisonous substances, if possible, by the bowel and urine, holds good. Where the patient's condition will not permit abundant administration of water by stomach or bowel, subcutanous injections of salt solution must be used to restore sufficient diuresis. Otherwise, the treatment is symptomatic, sedatives, such as bromides for restlessness and delirium, ice pills, cocaine, etc., for vomiting, and stimulants for heart weakness.

NATURE OF THE DISEASE.

Acute yellow atrophy holds a peculiar position among diseases of the liver on account of the great speed and degree of change in the liver cells. We have the striking picture of a large solid organ rapidly decreasing in size by the self-digestion of its cells and the appearance in the urine and blood of products of proteid digestion (leucin, tyrosin, etc.). The course of the disease has raised so many interesting questions regarding the functions of the liver and metabolism in general and its anatomical relation to other diseases of the liver, that it has attracted much greater interest and been far more carefully studied than other diseases of equal rarity.

Recent work on autolysis, the self-digestion of body cells, by Salkowski, Taylor, Jacoby and others, has thrown much light on the process of liver atrophy. Salkowski has shown that any aseptically preserved organ can undergo autolysis or self-digestion by its own ferments, if kept at body temperature, and produces substances similar to those of ordinary intestinal digestion including leucin and tyrosin. Autolysis has been found to be important in many pathological conditions, such as the absorption of exudates and of aseptic necrosed tissue. The necrosis in this disease apparently differs from ordinary necrosis in the rapidity and completeness of absorption of the dead cells. It resembles somewhat the resolution of a pneumonia.

The rapid disappearance of over one half of a

large solid organ like the liver within a few days strongly suggests a process of self-digestion of necrotic liver cells by their own ferments. This is explained by the supposition that the original poison causing the process has a very specific action on the liver cells and destroys their life without injuring the proteolytic ferments which they contain, and thus self-digestion occurs. This view that a cell may be killed and also be able to digest itself is borne out by the autolysis of tissue in infarctions. The autolysis and absorption in the liver would go on much more rapidly because the circulation is good and removes the products as fast as they are formed. On chemical analysis of the liver itself, in our second and fourth cases the distribution of nitrogen precipitable and nonprecipitable by phosphotungstic acid shows very clearly the presence of marked autolysis.

The poison must affect the other cells of the body to a much less degree than the liver, so that it is possible for the patient to survive the liver necrosis for a time, during which absorption goes on until there is finally so great a loss of liver tissue and functions that general toxemia results.

On the other hand, liver extirpation in animals by Nencki and Pawlow, Saleskin and Zaleski and others have shown that in certain cases, in spite of the absence of the liver, an abundant formation of urea occurs, and no appreciable change in the proportion of ammonia to the total

nitrogen and urea. This same condition is found in some cases of acute liver atrophy, so that in certain cases of this disease, at least, we must attribute the toxemia to some other cause than lack of urea formation in the liver.

It must be admitted that the etiology of the disease is unknown. No specific poison has been identified, and it is apparently possible for many poisons to produce this effect upon the liver under certain circumstances,— phosphorus, mushrooms, arsenic or chloroform perhaps (Ballin's 9 cases), the poison of syphilis and of some other acute infectious diseases; any poison in short that does not cause death at once, and at the same time injures the liver cells without destroying their ferments and thus causes autolysis.

From the fact that this disease is usually ushered in by disturbances of the digestive canal, and that the liver is the organ chiefly damaged, it has long been thought that the poison frequently may come from the bowels, and is a ptomaine or toxalbumin or bacterial toxin resulting from abnormal intestinal putrefaction or fermentation.

It is natural that such a violent acute disease should be considered an infection, but the bacteriology of the disease is very uncertain, the results of different observers conflict, sterile cultures are often obtained, and, in general, no organism has been found frequently enough to deserve special consideration. A few cases (Babes, Ströbe and von Kahlden) have been

reported of infection through the bile passages; this surely is an exceptional occurrence, the slight involvement of the bile ducts does not accord with an ascending infection or intoxication of this sort.

Quincke has advanced the theory that the changes of acute liver atrophy might be produced by a backing up of pancreatic juice into the liver and subsequent digestion of its cells as a result of obstruction to the common duodenal opening of the duct of these two glands.

This ingenious theory has many objections; only one or two cases have been reported in which any such obstruction was found. Opie has shown that the result of obstruction of the ampulla of Vater is not an escape of pancreatic juice into the liver, but the reverse, an escape of bile into the pancreas because the bile pressure is greater than the pancreatic juice pressure, which results in pancreatitis, fat necrosis, etc. Finally, Best's experiments of injecting trypsin into the liver by way of the bile ducts did not produce the typical changes of acute atrophy.

Now we turn to the chemical changes and symptoms which *result from* or *are associated with* the liver atrophy.

No change in the urine is more important than the diminished excretion of urea discovered by Frerichs, and the simultaneous appearance of leucin and tyrosin and other amino-acids, substances which are not normally found in cell metabolism or, if formed, are speedily changed into urea.

This lessened excretion of urea is almost invariably accompanied by a marked relative increase in the excretion of ammonia, a substance which is commonly regarded as a precursor of urea; and this double change is looked upon as a sign of liver insufficiency; hence the importance which is placed upon ammonia estimations in acute liver atrophy.

These facts are capable, however, of another interpretation. Increased *acid formation* may also increase the excretion of ammonia; and there is good evidence of this process in acute liver atrophy. Sarcolactic acid is present in large amounts in the urine, fatty acids are increased, and other abnormal acids such as oxymandelic and diacetic acids have been found.

Since the native alkali of the body is not sufficient to neutralize so much acid it apparently occurs in this disease, as in diabetes, that part of the NH_3 derived from proteid metabolism is diverted from its usual course and instead of contributing to the formation of urea is used to neutralize the pathological acids.

Münzer has shown that ammonia excretion in acute phosphorus poisoning is directly dependent on the acid formation in the body. He gave 6 gm. of sodium bicarbonate a day to a patient with acute phosphorus poisoning, with the result that the ammonia excretion fell rapidly. The fact that the increase of ammonia in this similar disease has been proved to be *for the purpose of neutralizing an acidosis* must show that it can no

longer be regarded as a clear sign of hepatic insufficiency.

The recent ideas upon the source of the amino-acids, leucin and tyrosin, are interesting and important. It has long been believed that these substances appear in the urine because of liver insufficiency. They were supposed to be formed in the bowel as the result of normal intestinal digestion and also in the tissues, and were carried to the liver, but were not converted into urea as they normally are, because of the damaged condition of the liver, and so passed to the kidney to be excreted.

The investigations of Jacoby, Schryver and Taylor on autolysis have placed this matter in a new light. It is probable that a large part at least of the leucin and tyrosin is formed by the self-digestion of the cells of the liver. Taylor has shown that these products of digestion can be found in considerable amount in the liver itself, in spite of the fact that the greater part of that formed must have been carried away by the blood. The quantities in the urine vary and the conditions which determine their appearance (greater or less destruction of the liver, poor excretion by kidneys, solubility, etc.) vary from case to case. The amount in the urine may be slight and yet large amounts may be obtained from the liver after death.

On the other hand, Neuberg and Richter have analyzed the blood from a case of acute liver atrophy, and found an amount of these substances

so large that it could only be derived from the autolysis of the entire liver, and as the liver is only partly destroyed it could at most furnish only a part of this large amount. The rest must be derived from the autolysis of other organs and tissues, or from the intestinal contents.

In short, it is difficult to tell just what relation the intestinal and hepatic disturbances bear to one another; but the leucin and tyrosin in the urine are probably derived partly (perhaps chiefly) from self-digestion of the liver, and partly from the amino-acids of the bowel and tissues, which the liver cannot transform into urea as it does normally.

The albumose in the urine which is occasionally present in this disease probably comes from the decomposing liver tissue.

The purin bodies in the urine come also from the destruction of nuclei in the liver.

The urine usually contains a large amount of bilirubin from which we must conclude that the production of bile pigment is kept up in spite of the severe damage to the liver.

When we attempt to explain the symptoms and course of this illness from what we know of its pathology we meet new difficulties. In fatal cases it is very hard to distinguish the disturbance of symptoms and signs due to the original infection or intoxication from those due to lack of liver function or to the flooding of the body with poisonous bile constituents.

The jaundice itself is at first probably due to

catarrh of the bile passages and later to plugging of the passages by desquamated cells and partial closure, by collapse and distortion of liver tissue.

Many attempts have been made until recently to prove that the salts of the bile acids are the chief cause of the severe symptoms. Bickel has recently shown that these bile acid salts are powerful poisons to the nervous system, but it is doubtful whether these substances are ever present in sufficient concentration to produce such results.

It seems natural to explain the hemorrhagic diathesis by the solvent action of bile acids upon red blood cells and the production of changes in the walls of the blood vessels. This is very doubtful, however, on account of the great dilution of the biliary salts in the organism. They are best explained by the general disturbance of nutrition.

The cholemia is probably the cause of some of the milder nervous symptoms, such as headache, malaise and weakness, also of slowing of the pulse, and of damage to the kidneys.

On the other hand, the *chief symptoms of severe intoxication* are largely due to the damage done to the functions of the liver and the special poisonous substances are probably

a. Nitrogenous antecedents of urea.

b. Certain products of decomposition in the bowel which are normally deprived of their toxic power in passing through the liver.

c. Decomposition products of the destroyed liver tissue.

This view is borne out by observation of other severe diseases of the liver where little or no jaundice occurs.

In closing I wish to thank Prof. Wm. T. Councilman, of the Harvard Medical School, for invaluable aid in the examination and interpretation of the histological sections of the liver and other organs, also Dr. Francis H. Williams, visiting physician at the Boston City Hospital, for the opportunity to study and report the third case, and Dr. Carl L. Alsberg, of the Harvard Medical School, for his assistance in certain of the chemical analyses and his kindly criticism of the chemical portion of this paper.

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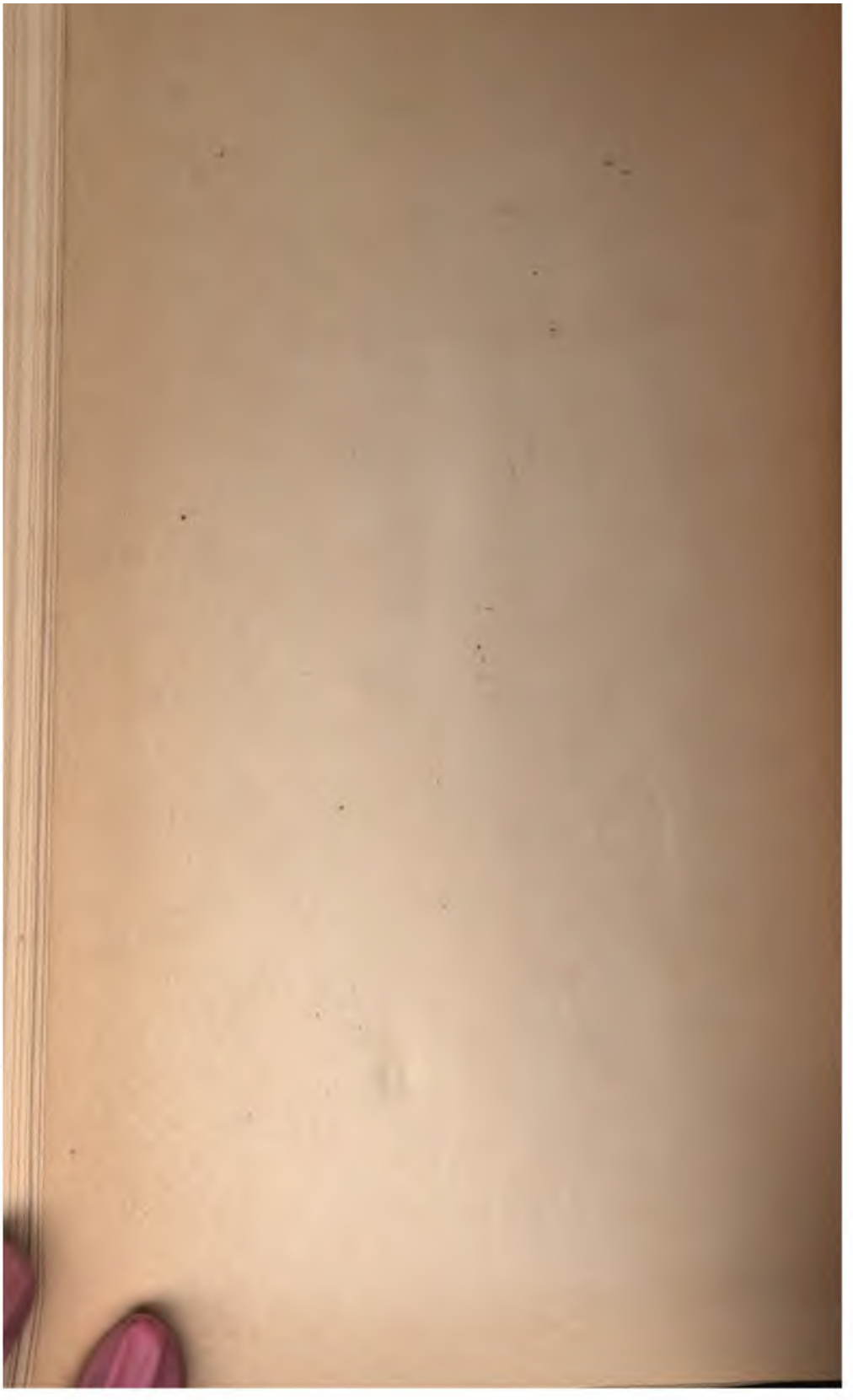

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